Vol. 37 AUGUST, 1950 No. 2

HOSPITAL LIBRARY
2/A1

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

Editor

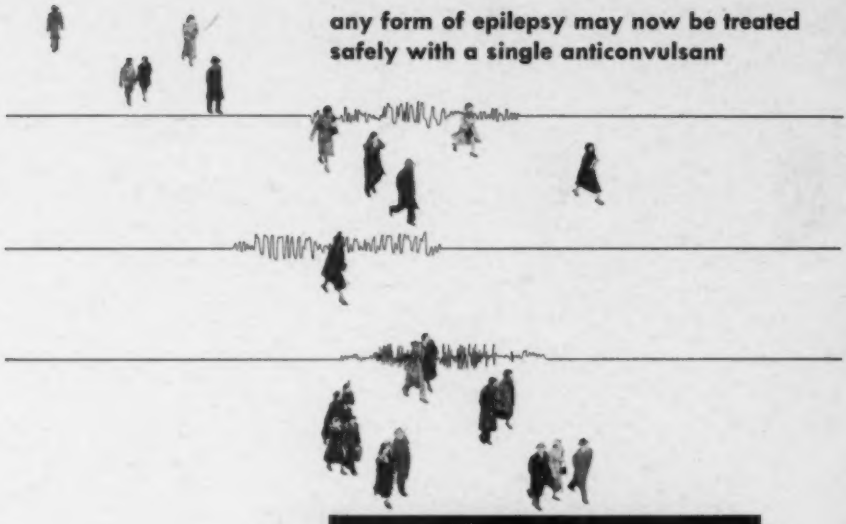
BORDEN S. VEEDER
St. Louis

Editorial Board

HARRY BAKWIN	New York
RUSSELL J. BLATTNER	Houston
ALEXIS F. HARTMANN	St. Louis
LEE FORREST HILL	Des Moines
CHARLES F. McKHANN	Cleveland
WALDO E. NELSON	Philadelphia
HENRY G. PONCHER	Chicago
EDWARD B. SHAW	San Francisco

Published by THE C. V. MOSBY COMPANY, 3207 Washington Blvd., St. Louis 3, U.S.A.
Copyright 1950 by The C. V. Mosby Company

Table of Contents on 3rd Cover



any form of epilepsy may now be treated safely with a single anticonvulsant

THIANTOIN SODIUM

(PHETHENYLATE SODIUM, LILLY)

No longer is it necessary to run the risk of bringing a second type of seizure into prominence by the selection of a limited anticonvulsant.

'Thiantoin Sodium' is a more widely useful antiepileptic and is far safer than related drugs of comparable potency. Many resistant cases are controlled with doses which have been elevated safely to levels that were previously unattainable.

Not only are there fewer side-effects, but there is often striking improvement of mental function in epileptic patients who receive 'Thiantoin Sodium.'

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

Complete literature on 'Thiantoin Sodium' is available from your Lilly medical service representative or will be forwarded upon request.

Vol. 37, No. 2, August, 1950. The Journal of Pediatrics is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: The United States, its Possessions and Pan-American Countries, $10.00 a year; Canada and other foreign Countries, $11.00 a year. Entered as Second-class matter June 29, 1932, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

The Journal of Pediatrics

VOL. 37 AUGUST, 1950 NO. 2

Original Communications

INTUSSUSCEPTION IN INFANTS AND CHILDREN

ANALYSIS OF 152 CASES WITH A DISCUSSION OF REDUCTION BY BARIUM ENEMA*

MARK M. RAVITCH, M.D., AND ROBERT M. MCCUNE, JR., M.D.
BALTIMORE, MD.

THE scope of pediatric surgery has been greatly increased by recent advances in pulmonary, esophageal, and cardiac surgery. Intussusception remains one of the most critical conditions with which the pediatric surgeon deals; one in which a considered and rational approach should eliminate fatalities—except for the most sadly neglected cases. Despite the fact that reported mortality figures remain high, there is great reluctance to accept the work of Hirschsprung and his Danish, Swedish, and Norwegian followers and Hipsley and his Australian colleagues who in vast numbers of cases long ago achieved mortality figures only being approached today.

We have analyzed in detail the records of 151 children below the age of 15 years who have been treated for intussusception at the Johns Hopkins Hospital from 1889 to 1948. The results have been studied in as many ways as seems profitable. The history on admission, the findings on examination, the treatment, and results are successively discussed. The recent changes in therapy which have eliminated mortality and drastically reduced morbidity are discussed at length.

INCIDENCE

One child had intussusception on two occasions and we therefore have 152 instances of intussusception.* Of these 152, in three instances color was not noted, 63.1 per cent were white children, and 36.9 per cent were Negro children. In 1947, white children made 40 per cent of all dispensary visits, and Negro children 60 per cent of all dispensary visits. This would therefore suggest that intussusception is somewhat more common in white than in Negro children. Male children suffered 62 per cent of the intussusceptions and female children 38 per cent of the intussusceptions. The ratio is almost 3:2, confirming previous reports which regularly show a male preponderance. No explanation has been offered for this sex selectivity.

From the Department of Surgery of Johns Hopkins University and Hospital, Baltimore, Md.

*Since these figures were computed we have had 18 additional cases, and no deaths.

As seen in Chart 1, intussusception occurs largely in the first year of life, and in that year most commonly in the period from the fifth to the ninth month. Of the 152 cases, 61 per cent occurred in children who were 4 to 11 months of age.

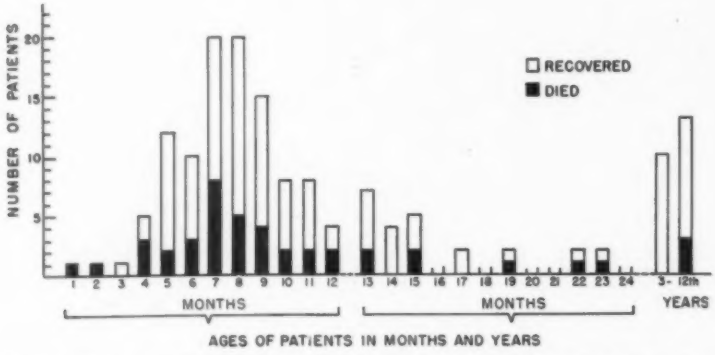


Chart 1.—Intussusception (1893-1948). Age Incidence Related to Mortality. The peak of incidence is in the 5- to 9-month age period and 61 per cent of the intussusceptions occurred in children from 4 to 11 months of age. Almost 90 per cent of the patients were under 2 years of age. Mortality is high in infants under 4 months of age and no children died in the 2- to 3-year-old group.

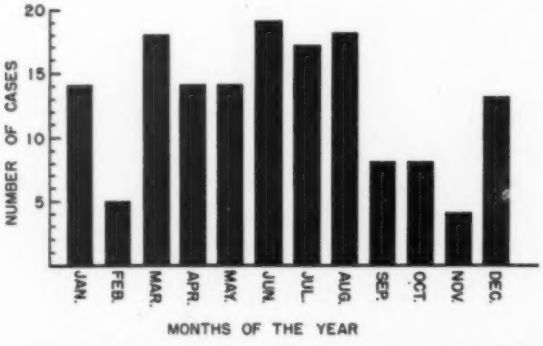


Chart 2.—Seasonal Variation of Intussusception (1893-1948).

Some writers have noticed a seasonal variation in the incidence of intussusception, usually finding the incidence maximal in the summer months and attributing this to the greater frequency of gastroenteritis in such seasons. As seen in Chart 2 in our material, there is a sustained peak from March through August and another in December and January. Chart 1 shows the maximal incidence of intussusception to be in the seventh, eighth, and ninth months of life. This seasonal variation in the incidence of intussusception does not merely reflect a corresponding peak seven to nine months previous in the local birth rate, since the number of live births in Baltimore from month to month, year in and year out, varies by no more than plus or minus 6 per cent.

PREDISPOSING CAUSES

As other authors have remarked, intussusception tends to select well-nourished infants. Of 119 cases in which notation was made of the state of nutrition, in 98 it was said to be good, in 11, fair, and in 10, poor. Similarly, of 142 cases in which the histories are adequate, it is found that in 74 cases, previous health had always been good. In 22 cases, diarrhea had been noted previously, in 13 cases, constipation had been a prominent feature, and in 10, there had been symptoms on previous occasions suggestive of intussusception. Search of the history for common predisposing causes was not particularly fruitful. There were 20 children who appeared to have had definite bouts of diarrhea before a sudden change in the character of the symptoms indicated the onset of intussusception. Four children received cathartics for constipation just before the onset of symptoms and three others had been severely constipated. Ordinarily, intussusception seemed to attack healthy children and to come out of a clear sky.

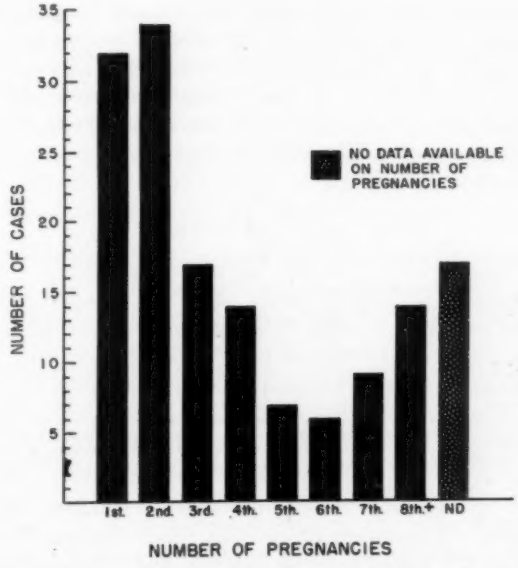


Chart 3.—Intussusception Relation to Parity. A surprising number of the children occupy late positions in their mothers' obstetrical careers.

Ten patients had histories which clearly indicated previous attacks of intussusception with spontaneous recovery. This is seldom commented upon in reports on intussusception and we were unprepared for this finding. The intervals between previous attacks and the intussusception which finally brought the patients to the hospital varied from ten days to six months. It is significant that 9 of these 10 children were operated upon and of these 9, in 3, polyps were found and removed. It is probable that a search for polyps should be made whenever there is a strong history of previous attacks.

Analysis of the maternal childbearing history reveals a surprising number of patients who occupied late positions in their mother's obstetrical careers. As shown in Chart 3, in 9 instances intussusception affected a child who was the seventh in his family and in 14 instances a child who was at least the eighth in his family. In 36/135 of the instances in which data are available, the child with intussusception was at least the fifth child in his family.

SYMPTOMS

The *chief complaint* in 44.1 per cent of the cases was vomiting, and in 42.8 per cent of the cases was the passage of blood per rectum. The patients being largely infants, only 25.7 per cent of the mothers considered abdominal pain the chief complaint. In some instances, pain and vomiting, or pain and bleeding, or vomiting and bleeding formed joint chief complaints. In the remainder of the cases, prolapse of the intussusception, distention, constipation, diarrhea, fever, prostration, and many other symptoms were variously given as chief complaints. As seen in Table I, evidences of abdominal pain announced the onset of intussusception a little more frequently than did vomiting, 71/152 or 46.7 per cent as opposed to 55/152 or 36.2 per cent. The appearance of blood per rectum was the first symptom in only 17/152 or 11.2 per cent. As might be expected, pain is increasingly the first symptom in successively older age groups while blood in the stool is the first recognized symptom almost solely in infants in the first two years of life when the less dramatic symptoms may not be brought to the mother's attention.

TABLE I. SYMPTOMS OF ONSET*

	0-2 (YEARS OF AGE)	2 AND OVER (YEARS OF AGE)	ENTIRE GROUP
Pain	53/129 = 41.1%	18/23 = 78.3%	71/152 = 46.7%
Vomiting	53/129 = 41.1%	2/23 = 8.7%	55/152 = 36.2%
Blood	16/129 = 12.4%	1/23 = 4.3%	17/152 = 11.2%
Refusal to eat	8/129 = 6.2%	1/23 = 4.3%	9/152 = 5.9%
Prolapse, restlessness, diarrhea, constipation, distention, nausea, listlessness, fever, and convulsion—			11.1%

*Pain is the commonest symtom at the onset of intussusception, vomiting next, and bloody rectal discharge, third. In the infants, pain was not appreciated by the parents as in the more articulate older children.

Vomiting.—In all, 141/152 or 92.8 per cent of children vomited before treatment was begun. There were 129 infants under the age of 2 years, and vomiting occurred in 122/129 of these or 94.6 per cent. In the children 2 years of age and over, 19/23 or 82.6 per cent vomited. As to the relation of vomiting to the time of onset of symptoms, it is found that 89/122 or 73 per cent of the infants under 2 years of age who vomited began to vomit in the first three hours of the disease, while in the children over 2 years, 10/19 or 52 per cent vomited in the first three hours. It would appear then that vomiting occurs most uniformly in the younger patients and that in these infants vomiting tends to begin earlier in the course of the disease.

The feeding history of the children after the onset of symptoms is of interest. Only 9/112 took and retained food while 47/112 took food after the onset of symptoms but were unable to retain it.

Blood.—In all, blood was seen in 138 of 152 cases, or 91 per cent. In 95 per cent of the 129 patients under 2 years of age, blood had been observed in stools or in the rectum, but in only 65 per cent of the 23 patients over 2 years old. In all, 79/134 or 59 per cent of those who showed blood (all ages) showed blood in the first twelve hours and 48/134 or 37 per cent of those who showed blood did so in the first three hours. There appears to be little difference in the appearance time of blood in the stool in the two age groups, although the younger children are more likely to show blood than are the older ones. The blood was prominently mixed with mucus in the great majority of cases. At times, the stools consisted almost entirely of mucus which was produced in great amounts with only a slight admixture of blood and occasionally with blood detectable only under the microscope. A few white blood cells were not uncommonly seen in the stool, but it was uncommon to see actual pus. In many cases, blood was detected only on the examining finger, further emphasizing the necessity for rectal examination.

Pain.—The history of apparent pain was obtained in 65/107 or 60.7 per cent of infants under one year of age, in 18/22 or 81.8 per cent of the infants one to two years of age, and 21/23 or 91.3 per cent of the children over two years of age. This presumably reflects equally on the articulateness of the patients and the acuteness of the mothers.

Constipation.—In 43 of the 152 cases, constipation was noted as a complaint, more commonly in the less articulate, younger patients. The absence of stools after the onset of symptoms is a negative symptom of some importance although it is not uncommon for the patient to evacuate his bowel at the onset of intussusception.

Diarrhea.—Diarrhea during the period of intussusception occurred in 11 or 7.2 per cent of the 152 cases. Nine of these 11 patients were under one year of age. This symptom may occur when obstruction to the bowel is still incomplete. Two of these 11 patients did not have a palpable mass on physical examination. Diarrhea occurs in intussusception with sufficient frequency to make it wise to consider the diagnosis of intussusception in infants presenting an atypical clinical picture of dysentery. Of these 11 patients, 5 were actually first mistakenly diagnosed as having dysentery and 3 died as a result of the ensuing delay.

Prolapse of the intussusception through the anus occurred in 7 children, an incidence of 4.6 per cent with no significant difference in incidence in different age groups.

Distention as a complaint was rare, being made only three times in all, each time in an infant.

Listlessness, drowsiness, or prostration were noted by the mothers in 30.0 per cent of all cases with no variation in distribution in the age groups.

Only one mother had felt a *mass* in her child's abdomen.

Physical Examination.—

Temperature: There were 97 children under one year of age in whom there were data on the temperature, and of these, 41/97 or 42 per cent had a temperature of 101° F. or above at the time of admission, 28/97 or 29 per cent

had temperature of 102° F. or over, and 12/97 or 12 per cent, 103° F. or over. In the one- to 2-year age group, 6/19 or 32 per cent with data had temperatures of 101° F. or over, and in the group over 2 years of age, 3/21 or 14 per cent had a fever of 101° F. or over. Fever is both commoner and higher in the younger patients.

There were 35 fatal cases in which the admission temperature was recorded. There were 15 children who had temperatures of 103° F. or over on admission and 11/15 (73 per cent) of these died. There were 4 who had a temperature over 104° F. and these 4 all died. Of the fatal cases, 23/35 or 66 per cent of the patients had a temperature of 101° F. or over. Thus, while in a third of the fatal cases on which there are data, the patients did have temperatures below 101° F., the presence of a high fever was of very grave prognostic significance.

In the records of the patients before reduction of the intussusception, pulse, and respirations are not regularly noted and no statistical studies can be made. In both features, the trend is toward elevation.

White Blood Cell Count: Of the 109 cases in which the white blood count is recorded before treatment, the count was 12,000 or over in 60 per cent, and 13,000 or over in 53 per cent. In 17 per cent, the white blood cell count was 20,000 or over.

Of the patients who died, the leucocyte count before treatment is recorded in 21. Of these, 14/21 or 67 per cent had counts of 12,000 or higher, but since 51/88 or 58 per cent of the survivors with data on white blood count had counts of 12,00 or over, the leucocytosis is of no prognostic significance.

Prostration.—Of the total of 152 cases, the history permitted evaluation of this symptom in 137. Of this group, 66/137 or 48 per cent presented the appearance of prostration. Of the 76 showing little or no evidence of prostration, 9/76 or 12 per cent died. Of the 66 noted to be prostrated, 28 or 42 per cent died. In 6 of the fatal cases, data were lacking as to prostration. Obviously the signs of torpor and depression are indicative of graver progression of the disease. There is no important variation in the significance of this symptom in the three age groups.

The appearance of prostration is fairly directly related to the duration of symptoms. Of 65 cases of prostration on which data were adequate,

5 occurred in 27 patients (18 per cent) who were ill six to twelve hours
10 among 25 patients (40 per cent) in the twelve- to twenty-four-hour group
9 in the 26 patients (35 per cent) in the twenty-four- to thirty-six-hour group
10 in the 11 patients (90 per cent) in the thirty-six- to thirty-eight-hour group
9 in the 19 patients (47 per cent) in the forty-eight- to seventy-two-hour group
10 in the 18 patients (55 per cent) in the seventy-two- to ninety-six-hour group
12 in the 24 patients (50 per cent) in the ninety-six-hour-and-over group.

As will be pointed out again later, mortality and severity of the disease vary directly with duration of symptoms for the first forty-eight to seventy-two hours after which the figures are weighted by the appearance of a number of cases of nonstrangulating chronic intussusception.

Dehydration.—Dehydration was found to be marked enough to be noted in 51/124 (41 per cent) of cases in which there was adequate data. Of these, 21 or 41 per cent died. There was no significant difference between the infants and the older children. Of the 73 children who were not dehydrated, 8/73 (11 per cent) died. Adequate data regarding dehydration were not given in 14 children who died. It seems clear that had adequate data been available in this group the grave prognostic significance of dehydration would be even more strongly emphasized, for as it is, only 8 patients died in whom the absence of dehydration was recorded on admission.

Associated Diseases.—It appears noteworthy that at the time of admission in 34/141 cases or 24.1 per cent of the patients in whom there are adequate data there was found either otitis media or an "upper-respiratory infection" or both on admission physical examination. A number of authors[6] have suggested that enlarged mesenteric nodes may be associated with upper-respiratory infections and in their turn cause the intussusceptions.

Examination of the Abdomen.—In a child with the characteristic picture of intussusception, the abdomen early in the disease, is flat or actually scaphoid. The intussusception occasionally forms a protuberance which is visible. Typically, the abdomen is very soft and nontender, although the child may wince when the intussusception is palpated and in such instances there may then be felt a litle muscular resistance over the mass. Palpation of the intussusception is the surest diagnostic sign and one should expect to palpate the tumor almost invariably. Early in the progress of a characteristic intussusception, the mass passes into the hepatic flexure behind the right costal margin and under the right lobe of the liver where it may be difficult or impossible to feel for some time. As time passes, the disease picture is confused by the superimposition of the nonspecific signs of intestinal obstruction: distention and intestinal patterns which may obscure the mass. In a number of instances, the mass was not definitely palpable until thrown into prominence by vigorous peristalsis during a cramp. The mass is usually described as tubular, sausage-shaped, or cylindrical. The pull of the mesentery on the intussuscepted bowel constrains the tumor to arch slightly in a curve.

Abdominal Resistance.—Of 124 cases with adequate data, 75/124 (61 per cent) of the patients were said to show complete relaxation of the abdominal wall with no resistance or spasm anywhere. Some resistance, even though only over the mass, was noted in 49/124 (40 per cent). Tenderness was noted in 45/111 or 41 per cent of those with adequate data. In most of these the tenderness was noted directly over the mass. It will be seen that the figures are almost identical for the incidence of resistance and of tenderness. Presence or absence of distention was remarked upon in 139 cases. In 49/139 or 35 per cent, a rather higher incidence than might be expected, distention was present.

Mass.—Data were adequate in 149 cases. In 132/149 or 89 per cent, a mass could be felt either abdominally or rectally. In 17/149 or 11 per cent, no mass could be palpated either abdominally or rectally. Of the 149 cases, 126 or 85 per cent had abdominal masses. In 91 per cent of the cases in which a mass was felt abdominally, the examiners were unequivocally certain that a mass was present. The abdominal mass was visible in 6 of 126 patients who had palpable masses and in whom descriptions were adequate.

Rectal examination was recorded in 124 cases. Of these, 48 patients (39 per cent) had masses palpable rectally. It is notable that in 6 cases, rectal examination revealed a mass which could not be felt by abdominal palpation.

Peristalsis.—Mention of presence or absence of visible peristalsis was made in 135 cases. It was noted to be present in 24/135 cases or 18 per cent.

Prolapse.—In 11/152 or 7 per cent of the cases, the intussusception presented at the anus or beyond. It is customary to warn against mistaking intussusception for a mere rectal prolapse in which obviously the finger cannot be passed between the prolapsed bowel and the nonexistent sheath; quite apart from the wide difference in the clinical picture in the two conditions.

Duration.—The age of the pathologic process is an obvious determining factor in the production of necrosis of the bowel and other physiologic disturbances. It is of interest, therefore, that in the last thirty years, the promptness with which children with intussusception are brought to our hospital has changed only a little, while our hospital mortality for the disease has dropped a great deal without reference to the fluctuation in the average duration of symptoms. A few cases of more than seven days' duration are accepted as being typical chronic intussusceptions, which might weight the results. In the period 1893 to 1909, patients averaged two days, eight hours from the onset of symptoms to beginning of definitive therapy, and in the period 1910 to 1919, the time was two days, six hours. In the next decade there was substantial improvement to one day, twenty-one hours. However, the periods in 1930 to 1939, and 1940 to 1948, were one day, four hours, and one day, twelve hours.

TABLE II*

DATE	ONSET TO TREATMENT (HR.)	ADMISSION TO TREATMENT (HR.)	MORTALITY (%)
1893-1909	56	2 + 15/60	75
1910-1919	54	2 + 27/60	41
1920-1929	45	2 + 36/60	41
1930-1938	28	1 + 45/60	29
1939-1948	38	2 + 16/60	9.4
Primary barium enema—26 hours		One hour, 7 minutes and if one case undiagnosed for 8 hours be excluded, the average period from admission to definitive therapy is 52 minutes—mortality 0	
Primary operation—43 hours		4 hours, 7 minutes—mortality 24	

*Since these figures were compiled, we have had 18 more cases of intussusception with no deaths. Two were operated upon primarily under a mistaken diagnosis, and 16 received primary barium enema therapy.

Chart 4 shows the relation of mortality to the duration of disease before the onset of definitive treatment. It is obvious that there is direct relation until one reaches the group with symptoms of over ninety-six hours' duration. It

is apparent that many of the children still alive with intussusception untreated for over four days must have had nonstrangulating obstructions and that these, carrying a better prognosis than the ordinary intussusceptions, tended to decrease the mortality in this group. Only 4/52 children treated in twenty-four hours or less succumbed, a mortality, since 1893, of 7 per cent. In the twenty-four- to forty-eight-hour group, 10/37 died, or 27 per cent. In children in the forty-eight- to ninety-six-hour group, 20/37 died, a mortality of 54 per cent, but in children definitively treated more than ninety-six hours after the onset of symptoms, only 7/23 died or 30 per cent.

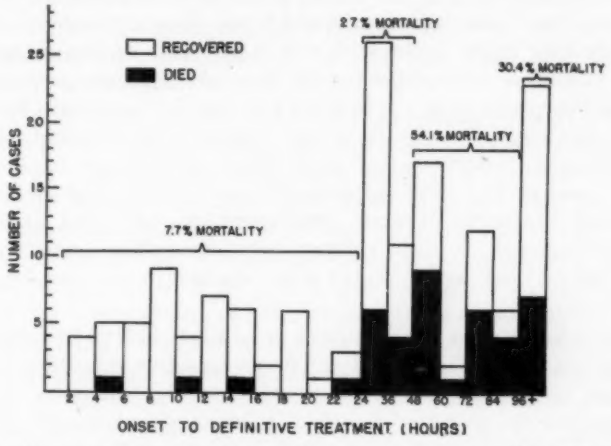


Chart 4.—Intussusception Relation of Mortality to Duration of Symptoms (1893-1948). The deaths in the group of patients seen in the first twenty-four hours all occurred more than twenty-five years ago. The mortality rises steeply in the succeeding hours and drops suddenly after ninety-six hours. This is due to the appearance at this point of cases of nonstrangulating "chronic" intussusception.

TREATMENT

A good deal of emphasis is often laid upon the necessity for swiftness in operating upon children with intussusception. The high mortality in some reported series and the low mortality in others have been ascribed to the promptness or tardiness in the diagnosis of the intussusception and to the swiftness with which operation is performed. While it is obviously advantageous to relieve intussusception as rapidly as possible, our data suggest that the employment of supportive measures followed by correct specific therapy is of greater importance than a delay of even several hours.

Thus the mortality has dropped steadily, apparently without reference to an increase in the last ten years in the time required to bring children to operation after admission to the hospital.

The average period, fifty-two minutes (*v.s.*), from admission to the hospital to institution of barium enema in the years 1939 to 1948, reflects the time involved in registering a child in a teaching dispensary, demonstrating to students and house staff, and going through channels to secure a surgeon. In the case of a private patient treated since these figures were compiled, we

were notified by phone that an infant with intussusception was en route. We were ready in the fluoroscopic room when the child reached the hospital. A mass was readily palpable in the right-upper quadrant. There was bloody mucus on the diaper. A barium enema was given at once and an intussusception of six hours' duration immediately reduced from the splenic flexure through the ileocecal valve. The child was sent to his room with the intussusception reduced less than ten minutes after the parents had brought him to the hospital gate.

Long delays in therapy, when they occurred, were the result of failure to diagnose intussusception. At times, a mistaken diagnosis of dysentery was made. At other times, dispensary physicians delayed treatment for lack of a sufficiently high index of suspicion. It is here that barium enema has a large field of usefulness in establishing the diagnosis of intussusception when it is otherwise difficult to make. It is a sad fact that in the period 1939 to 1948, five children died of intussusception in the Johns Hopkins Hospital. Four of these were sent home from the hospital untreated at the first visit for intussusception. The fifth was a child with polyposis of the entire gastrointestinal tract[7] who was already extremely ill when intussusception supervened. Our death rate, had intussusception in these children been recognized promptly, in our own hospital would have been expected to be less than 2 per cent for this ten-year period.

In the earlier cases, operation was undertaken with no preliminary preparation. In the Johns Hopkins Hospital, preoperative subcutaneous fluids were first given to patients with intussusception in 1918. An intravenous injection of electrolytes was first used in 1923. It gradually became the custom to give intravenous fluids or blood or both while preparations for operation were underway. With the barium enema treatment, intravenous fluids are not administered before therapy unless the baby is dehydrated or particularly prostrated. If intravenous fluids or blood are required, these are administered at once and the baby fluoroscoped and the intussusception reduced while the fluid or blood is being administered. Most infants, after barium enema reduction, take fluids hungrily by mouth and rarely require more than one parenteral administration of fluids.

The great bulk of the cases here reported were ward patients treated by the resident house staff. Until 1939, immediate primary operation was the procedure of choice excepting only one or two instances in the first years of the hospital's history, when operation was deliberately withheld.

Study of the types of operation performed and the results achieved has proved worth while.

Simple Reduction.—In the group of those operated upon primarily, there were 77 patients in whom no more than a reduction of the intussusception was done. Of these 20/77 or 26 per cent died. Before 1930, 14/40 or 35 per cent died. Since 1930, 6/37 or 16 per cent died. Since 1939 there have been no deaths in the 9 patients who required only a simple operative reduction of the intussusception.

Reduction with Excision of Local Lesions.—In 3 patients, a local lesion (2 polyps, 1 Meckel's diverticulum) was excised after the intussusception had been reduced. All survived.

Resection and Anastomosis.—In 9 instances, bowel was resected and an immediate anastomosis performed. Of these patients, 7/9 or 77 per cent died. The first of these, in 1899, died of a breakdown in the anastomosis. The next two died a few minutes and a few hours respectively after operation. The fourth, a one-year-old infant, recovered. The fifth died two hours after operation and the sixth recovered. The seventh died of peritonitis eight hours after operation. The eighth died of peritonitis sixteen hours after operation but with an intact suture line. The ninth was already moribund with polyposis of the entire gastrointestinal tract and succumbed twenty-eight hours after operation without peritonitis or gangrene.

Thus, of the seven patients who died after resection and primary anastomosis for an irreducible intussusception, only one, in 1899, died of an obvious failure of the suture line, and one died sixteen hours after operation of peritonitis with a grossly intact suture line. Four died very shortly after operation and it would appear, indeed, that most of the deaths were due to the disease and not to the treatment, although an ileostomy might conceivably have relieved pressure on the proximal bowel, and so more rapidly restored it to normal.

Reduction and Enterostomy.—In four cases, the intussusception was reduced and an enterostomy was performed at the site of intussusception or proximal to it. All four of these patients died, two before 1930 and two since.

Reduction and Extraperitonealization.—In one early case the reduced bowel, being of questionable viability was extraperitonealized. The patient died.

Reduction Plus Inversion.—In seven instances, the operator chose to invert an area of dark bowel of questionable viability rather than perform a resection. Three of these seven or 43 per cent died. Before 1930, 2/3 or 66 per cent of such cases died. Since 1930, 1/4 or 25 per cent died. All three of these deaths were in the immediate postoperative period and all apparently were due to the desperate condition of the patients at the time of operation.

Mikulicz Type Resection.—Before 1930, there was one such operation, which resulted fatally. Since 1930, of seven patients so treated, one died, a mortality of 14.3 per cent. Since 1939, three patients were so treated and all survived. Five of the resections were of the ordinary Mikulicz type, the bowel being amputated outside the body with the clamps left on the adjacent loops. Three of the operations were done by the modification described by Woodhall.[8] It is interesting that the two deaths occurred two to three hours after operation, being apparently attributable to the original disease and to the operation, and not to the loss of fluids from the ileostomy. In two cases, the detailed operative notes are missing and the precise type of operation performed cannot be determined. On the other hand, the fear of ileostomy in infants is perhaps unjustified. In all, eight children had a resection and an enterostomy. Two such children died. One, in 1928, had an exteriorization and resection and died in three and one-half hours. The only other death, in 1932 after a similar pro-

cedure, occurred three hours, forty-five minutes after operation. Both these deaths were probably unavoidable. The first patient of these eight received no blood but had a resection of the ileum and the colon and required numerous operations over a period of eight months before continuity was restored. The next two were operated upon by Woodhall with the lateral anastomosis and double-barrelled enterostomy described by him and both recovered. The fecal fistulas were closed twenty-one and eleven days after the primary operation. Neither of these fistulas was anything but a vent and the bulk of the intestinal secretions remained in the alimentary canal. The sixth child had a resection and a side-to-end anastomosis with the end of the ileal segment brought out as an ileostomy, a variation of Woodhall's procedure. This fistula was closed seven days later. The seventh child, 10 months old, had a massive resection and the two bowel ends, ileum and sigmoid, left open. Sixty days later, an ileosigmoidostomy was performed. This child's condition was precarious in the interval between operations. The eighth child, at the age of 9 months, had a resection and double-barrelled ileostomy. Fluid balance was never a problem and the bowel was anastomosed on the thirty-second day. Thus, of the six survivors, three had anastomoses with complementary vents, and three had both bowel ends brought out into the wound with no attempt at anastomosis.

Most authors advise against appendectomy at the time of operation. We have rather tended to feel that in children not too desperately ill, it is as well to remove the appendix if the abdomen is to be opened. In all, 28 patients had appendectomies in addition to whatever other operative procedure was required, and 2/28 or 7 per cent died. One of the deaths occurred in a very ill child who had an ileal resection to which was added an appendectomy, death resulting a few hours later. The other death occurred five hours after operation also in a very ill infant. It seems improbable that two or three minutes of additional operating caused death in these children, and in the other 26 certainly no ill effects were noted. On the other hand, in the desperately ill it is probably as well to avoid any unnecessary manipulations.

In 3 cases, the intussusception was found reduced at operation.

Four patients died without treatment and intussusception was disclosed at autopsy.

It would appear then that if a resection is to be performed, the result may perhaps be better if some form of enterostomy is performed with or without primary anastomosis. This finding surprised us, for we tended to be of the opinion that in modern-day surgery, time can always be taken for a primary anastomosis and the patient, particularly an infant, may be expected to do better if the intestinal continuity has been restored and ileal secretions are not lost. One would expect further that the use of penicillin and streptomycin would increase the likelihood of successful anastomosis and that blood, plasma, and indwelling intestinal tubes would further ensure recovery.

Mortality with Relation to Position of Intussusception.—Figure 1 shows diagrammatically the relation of mortality to the position of the intussusception. There are 137 cases in which accurate information is recorded. It will be noted

that death occurred most commonly in two groups: those intussusceptions still in the small bowel or cecum, and those which had reached the rectum and sigmoid. The probable explanation for the first group is that the intussusceptions began well up in the small bowel with an attendant earlier gangrene. In the second group are obviously those intussusceptions which had progressed the farthest.

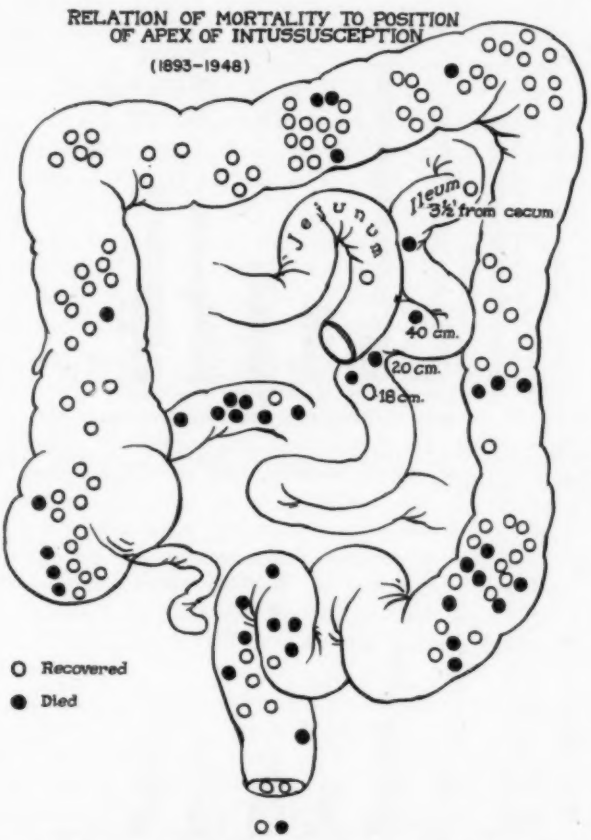


Fig. 1.—Deaths are commonest in intussusceptions reaching the rectum (the cases of longest standing), and in intussusceptions remaining in the ileum, where diagnosis is difficult and intestinal obstruction more serious.

At operation, free fluid in the peritoneal cavity was encountered in 35/88 or 40 per cent of the cases in which there is data on this feature. In 5/35, the fluid was bloody. Two of these had gangrenous bowel and three had viable bowel.

Chart 5 shows the relation of the duration of symptoms of intussusception to the condition of the bowel. As would be suspected, in the intussusceptions less than twelve hours old, the bowel is always viable, and the proportionate

incidence of gangrene rises steadily until in the seventy-two- to ninety-six-hour period the ratio of gangrenous to viable bowel is more than 2:1. After ninety-six hours, the ratio reverses itself. It is plain that if a child survives four days of intussusception it is likely to be because he has a combination of anatomic circumstances which militate against strangulation of the bowel so that these cases begin to border on "chronic intussusception."

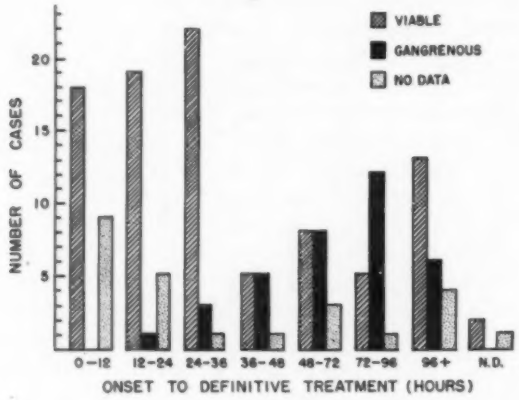


Chart 5.—Intussusception Duration of Symptoms Related to Viability. As in Chart 4 the "improvement" after ninety-six hours is indicative of the appearance of cases of non-strangulating "chronic" intussusception.

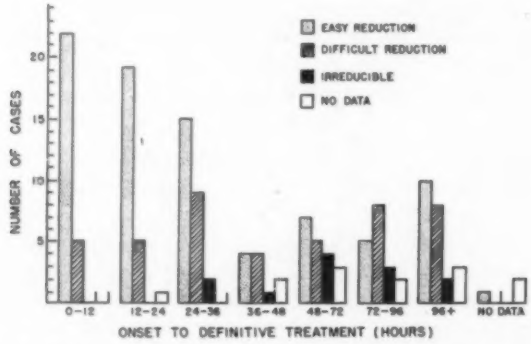


Chart 6.—Intussusception Duration of Symptoms Related to Reducibility.

Chart 6 shows the relation of the duration of symptoms to the ease of reducibility. The findings are parallel to those in Chart 5 of the relation of duration of symptoms to the viability of the bowel. Up to ninety-six hours there is a steady increase in the percentage of intussusceptions difficult to reduce or irreducible. After ninety-six hours, for the reasons mentioned above, irreducibility and difficulty in reduction are less common. These factors, taken

in conjunction with the findings stated earlier relative to dehydration and prostration, which are prominent features in the group with symptoms of ninety-six hours' duration or more, suggest that in this group there is every reason to delay operation until blood and fluids have been administered since intestinal obstruction is apparently a more serious factor than gangrene of the intussusceptum.

Chart 4 shows the relation of mortality to the duration of symptoms. It will be seen that 54/152 patients were treated twenty-four to sixty hours after onset of symptoms. In the first twenty-four hours, the mortality is 8 per cent in 52 cases (the 4 deaths occurred in 1893, 1914, 1915, and 1924—all more than 20 years ago). In the next twenty-four hours, the mortality is 27 per cent of 37 cases, and in the forty-eight- to ninety-six-hour group, between two to four days, the mortality rises to 54 per cent of 37 cases. After this, in line with the data given previously, mortality drops to 30 per cent.

Chart 1 shows the incidence of fatal cases in the various ages. The chief points of interest are the high mortality in infants under 4 months of age and the absence of mortality in the 2- to 3-year-old group. The peak incidence of the condition is seen to be in the 5- to 9-month age group.

Significance of the Type of Intussusception.—In 123 cases, data appeared adequate for classification of the lesion. Fourteen intussusceptions arose high in the ileum. Ninety-six arose in the terminal ileum or at the ileocecal valve, 6 arose in the colon, and 7 were said to be compound ileo-ileocolic intussusceptions. It is interesting to note that 10/14 or 71 per cent of the patients with ileal intussusceptions died and 24/96 or 25 per cent of the ileocecal variety. In the latter, one would expect obstruction to be less severe and strangulation to be less likely, due to the more distal segment of bowel involved and the greater diameter of the intussuscipiens. In general, we feel it of little value to differentiate between intussusceptions more precisely than: (1) those arising in the ileum, (2) those arising at or near the ileocecal valve, and (3) those arising in the colon.

Various authors give different figures for the incidence of specific lesions causing intussusception. Of our own series, 8 children or 5 per cent had such specific lesions. In 5, there was a polyp, in 2, a Meckel's diverticulum,* and in one, an ectopic focus of pancreatic tissue. It is significant that only 2 of these 8 patients were less than one year old, (6½ months and 10 months, respectively), 3 were over one year old, one was 2 years old, one almost 6 years old, and one 11 years old. In 2 of the 5 children who had polyps, the polyps were excised; in one, the type of operative procedure is not described, in one, the involved segment was resected and that baby died (of polyposis of the entire gastrointestinal tract) and one died on the operating table before operation could be performed. In 2 patients, a Meckel's diverticulum was found. Both patients survived—one after amputation of the diverticulum, and one after resection of the segment of the bowel from which the diverticulum arose. A 10-month-old infant with a

*In 2 of the 18 intussusceptions seen since this was compiled, there was a Meckel's diverticulum, and in another an intestinal duplication beneath the ileocecal valve.

fifty-hour-old intussusception due to a nodule of ectopic pancreatic tissue had a bowel resection and died. In general, the specific lesions are rare and, except in the desperately ill, should be excised if encountered at operation. In older children with intussusception or in any child with a recurrent intussusception, the possibility of such a lesion must be considered. Of 47 children over one year of age, 6 or 13 per cent had such mechanical lesions. However, only 2/105 or 1.9 per cent of intussusceptions in children under one year of age showed such lesions.

COURSE

Diarrhea, in the postreduction course is occasionally troublesome and creates suspicion that all is not well. Of all the 152 patients, 36 died in the first forty-eight hours, and there are no data for one more, leaving 115 cases. Of these, 26 or 23 per cent developed diarrhea of a significant degree, one of them on the tenth day after operation. Of these 26, 15 were patients who had an infection somewhere, such as upper-respiratory infection, wound infection, and other infections.

Stool cultures were made in only 6 patients with diarrhea. Of these, 2 showed Flexner's bacillus and one showed *Bacillus pyocyaneus*. It is fairly clear then that the traumatized bowel left by the reduction of an intussusception often responds with diarrhea and occasionally acts as a *locus minoris resistentiae* for pathogenic organisms. Diarrhea occurred after barium enema reduction in 4/32 or 13 per cent of the patients, but in 22/83 operative reductions or 27 per cent. Presumably the greater trauma of operative reduction accounts for the increased likelihood of postreduction diarrhea.

Ileus, after reduction, occurred in 7 per cent of the cases reduced primarily by operation, but in none of those treated primarily by barium enema. Postoperative distention occurred in 38 patients of whom 2 had had barium enema with operative completion of the intussusception, the remaining 36 having been treated by primary operative reduction.

Vomiting.—Postoperative vomiting of a significant degree occurred in 22.6 per cent of the children on whom there are data. All of these were treated by primary operative reduction.

Postoperative Fever.—There were 131 patients with postoperative fever or 90 per cent of all the cases. In 36/94 or 38 per cent of the cases with fever that did not die within five days after operation and in whom data were adequate, the fever was associated with an obvious wound infection, or with phlebitis. In 58/94 or 62 per cent there was no such association. Comparing the barium enema and primary operative groups, we find that only 4/114 or 3.5 per cent of the patients with data in the primary operative reduction group escaped postoperative fever, but 11/32 or 34.4 per cent of the barium enema group had no fever after reduction. In the period, 1939 to 1948, there were 24 children with primary operative reduction who had postoperative fever but no wound infection or phlebitis, and as it happened, 24 children also in the primary barium enema group who similarly had fever without obvious cause. In the primary operative reduction group, these cases of postoperative fever

without cause represented a total of 84 patient days of fever. While in the comparable primary barium enema group, these represented a total of but 35 patient days of fever.

Wound Infections.—Of 105 operative cases in whom there is adequate data on wound healing, 20 per cent developed wound complications—from mild infections to fecal fistulas.

Hospital Stay.—In the period, 1939 to 1948, the primary operative patients, excluding those who died, stayed in the hospital an average of 32.4 days. The barium enema patients averaged 8.8 days. The barium enema patients who were also operated upon, averaged 12.6 days, but those patients who were cured by barium enema, alone averaged only 5.8 days in the hospital.

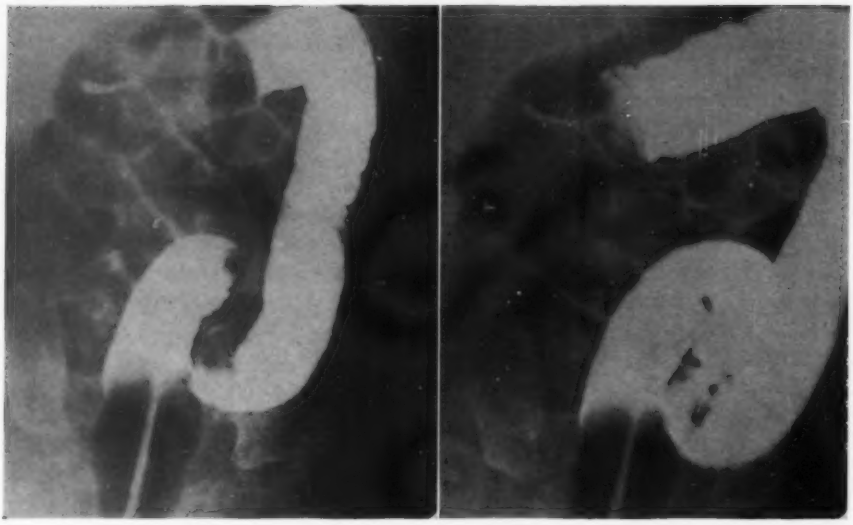
After reduction, there were 4 recurrences, 3 of them after operation. Of these 3, 2 were allowed to die without reoperation while one was reoperated upon, was found to have gangrenous bowel which was resected with recovery of the patient. One recurrence occurred after a barium enema reduction. After reduction, the child had taken feedings without vomiting, was having normal stools, and had passed the orally administered charcoal per rectum. The intussusception recurred, was reduced again to the cecum with barium enema, and the child taken promptly to the operating room where the base of the appendix was found intussuscepted in the cecum and easily reduced, the appendix then being resected. The child recovered without incident.

In 12 cases, mechanical intestinal obstruction developed weeks, months, or years after reduction, usually due to adhesions. In all of these patients, reduction had been by primary operation, except for one child, who 2 days after successful barium enema reduction, had a resection of the right colon because the edematous and palpable bowel was mistakenly thought to be involved in a diffuse tumor process. Three of these patients with intestinal obstruction recovered without operation. One died without operation and 2 died after operation.

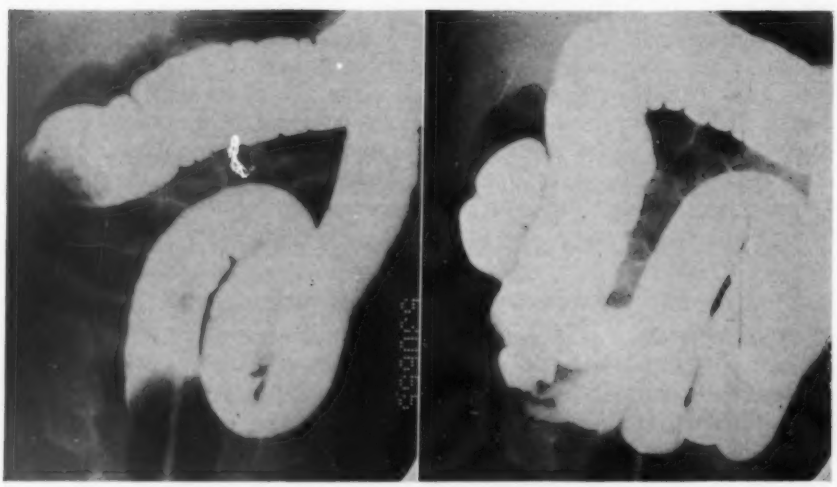
TECHNIQUE OF ADMINISTRATION OF BARIUM ENEMA

It is our feeling, at present, that the best treatment for intussusception in infants and children is radiologically controlled hydrostatic pressure reduction, followed by operation, if necessary to confirm reduction, or to complete the reduction if the intussusception persists. It has been our policy to apply hydrostatic pressure reduction to all children with intussusception regardless of the duration of the intussusception. The clinical and experimental evidence[9, 10] would indicate that with the method to be described, there is little or no danger of reducing bowel which is gangrenous, and little or no danger of rupture of the bowel. The Danish and Australian investigators who pioneered in the use of this method have, with their followers, treated many hundreds of patients, providing an impressive statistical testimonial.

As soon as the diagnosis of intussusception is made or suspected, the operating room is advised to prepare for operation. The infant is taken at once to the fluoroscopic room in the outpatient department and a Foley bag catheter with 45 c.c. balloon is inserted into the rectum and the balloon distended. It



A. *B.*



C. *D.*

Fig. 2.—Intussusception of 6 hours in a 4-month-old infant. There was a palpable mass in the epigastrium and a typical history. A Foley bag catheter has been placed in the rectum, the balloon distended, and barium allowed to run in with the reservoir 3 feet above the fluoroscopic table. In this instance, spot films were taken at intervals. The intussusception was reduced within fifteen minutes of the child's arrival to the hospital.

A, The barium column is arrested in the left transverse colon. Many loops of dilated, gas filled, small bowel are visible. The barium pushes forward in a thin shell around the end of the intussusceptum to produce the characteristic concave meniscus.

B, Reduction has proceeded almost to the splenic flexure. A little barium fills the lumen of the tip of the intussusceptum. This is uncommon.

C, The reduction has reached the ascending colon. The concave advancing edge of the barium column is plain.

D, Complete reduction. The cecum and appendix have filled and barium has run freely into distended loops of small intestine. The child fell asleep at once. No mass was palpable. Powdered charcoal was instilled in the stomach and recovered by enema six hours later.

is essential that the catheter be ungreased so that it may be less readily expelled. It is further essential that an assistant maintain firm pressure upon the buttocks, squeezing them together around the catheter throughout the procedure. The reservoir, filled with a thick suspension of barium, is elevated to 3 feet above the table and the barium permitted to run into the bowel under fluoroscopic observation. The barium will usually be seen to run rapidly into the rectum and colon until the head of the barium column meets the point of the intussusception. At this point, the rounded head of the advancing barium column suddenly becomes concave forming a meniscus around the point of the intussusception, much as would a column of barium in the vagina outlining the cervix. As pressure increases, the meniscus lengthens, the horns extending until suddenly the intussusception is pushed back and the meniscus flattens out again (Fig. 2). This process is repeated sometimes with extreme rapidity until the intussusception is reduced to the cecum and through the ileocecal valve. One should take care to see that the barium flows freely into the ileum. In one instance we observed that the barium passed 3 or 4 inches up into the ileum and then stopped while the characteristic meniscus was still discernible. This child was taken at once to the operating room and found to have an intussusception in the ileum about 6 inches above the ileocecal valve, the reduction of which was readily completed.

At times, the entire reduction proceeds swiftly and smoothly, and at others the reduction hangs at one point or another until the intussusception suddenly gives way. If the intussusception is not completely reduced after several minutes, the catheter is removed and the infant permitted to expel the barium, after which the catheter is reintroduced and the bowel distended once more. We do not feel justified in doing this more than three times in all. Thus far we have never failed to reduce the intussusception, at least to the cecum. As seen in Fig. 3, intussusceptions have been completely reduced even when the intussusception presented at the anus. It is important to be satisfied that the barium has gone through the ileocecal valve into the ileum and that the intussusception has been completely reduced. The distended cecum and the sigmoid, if redundant, may overlap obscuring the field so that it is difficult to see the ileum. In such instances it is permissible to displace the cecum with the hand or to turn the child upon the abdomen, thus letting the child's own weight displace the bowel. In one infant, inadvertently, we filled almost the entire small intestine with barium before realizing that the intussusception had been completely reduced.

Immediately after the completion of the reduction, powdered charcoal is deposited in the patient's stomach through a tube and six hours later an enema is administered to recover the charcoal and prove, beyond doubt, the completeness of the reduction. The successful reduction of an intussusception is indicated by the following criteria: (1) the entrance of barium well into the small bowel, (2) return of the barium with feces or with flatus, (3) disappearance of the mass, (4) clinical improvement of the child who often falls into a natural sleep, and (5) subsequent recovery in the stool of charcoal given by the mouth

or the appearance of a blood-free stool. Since 1939, 32 patients have had primary treatment with barium enema. All 32 survived. In 22 cases, the intussusception was reduced by barium enema alone. In 9 cases, operative completion of the reduction was required, usually through a McBurney incision.* In one case, a resection was performed although one of us stated that the bowel was viable and microscopic sections showed it to be so.[9] Sulfasuxidine or streptomycin is administered orally for several days as a prophylactic against specific enteritis. We feel strongly that hydrostatic pressure reduction should be undertaken by the surgeon whose responsibility it is to decide whether open operation is to be performed.

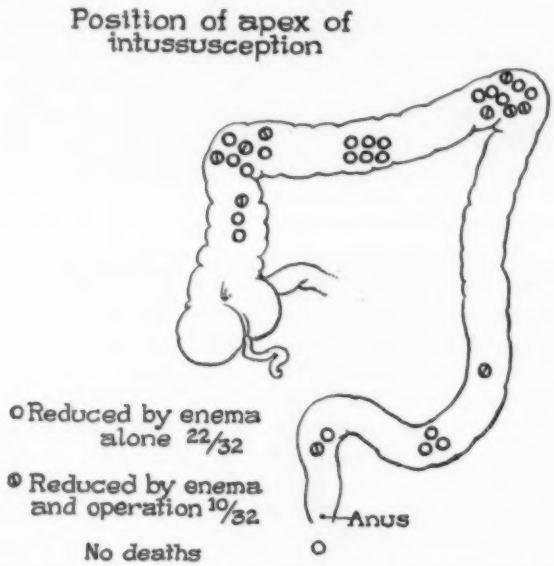


Fig. 3.—In the period from 1939 to 1948, 32 children were treated by primary barium enema reduction. There were no deaths. In 22 cases, enema alone was all that was required. In the remaining patients the intussusception was reduced to the cecum by the barium enema, and reduction was completed at operation, usually through a McBurney excision.

Since this chart was drawn, the addition of 16 more cases of intussusception makes a total of 48 cases:-33/48 (69 per cent) reduced by enema alone, 15/48 reduced by enema and operation, and no deaths.

Hipsley,[5] who has had very great experience with the reduction of intussusception by hydrostatic pressure, uses an ordinary enema without fluoroscopy, but relies on an additional criterion. If the intussusception has been reduced after the bowel has been distended with saline solution, a good deal of the fluid passes through the ileocecal valve into the small bowel. This fluid will then be retained, even after the child has emptied its colon following reduction. Hipsley measures the abdominal girth before and after reduction, and if after the putative

*Since these figures were compiled, we have treated 16 additional cases of intussusception by barium reduction. The results for the entire series are: 48 cases, 33 reductions by enema alone (69%), 14 reductions by enema to the cecum or ileocecal valve, and one to the ascending colon completed at operation; no deaths.

reduction the abdominal girth is increased, he assumes that it is due to the fluid retained in the ileum, thus indicating reduction. We have made a mistaken diagnosis of complete reduction in only one instance. On that occasion the intussusception was apparently reduced only to the cecum. Symptoms recurred within a few hours on the ward. The intussusception was again reduced to the cecum and the reduction completed by an open operative procedure.

SUMMARY

Intussusception is a condition which should be free from mortality if treated in the first twenty-four hours after onset of symptoms. Preoperative administration of parenteral fluids and blood is of sufficient importance to warrant priority over definitive therapy, especially in late cases. Hydrostatic pressure reduction under fluoroscopic control appears to give both a lower mortality and a lower morbidity than primary operative reduction as measured by fever, diarrhea, vomiting, distention, length of hospital stay, wound infections, and mechanical intestinal obstruction due to adhesions. If resection is required, anastomosis with an associated vent seems the safest method.

REFERENCES

1. Hirschsprung, H.: 107 Falle von Darminvagination bei Kindern behandelt in Königin Louisen Kinderhospital in Kopenhagen während der Jahre 1871-1904, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**: 555, 1905.
2. Monrad, S.: Acute Invagination of the Intestine in Small Children, Acta. Pædiat. **6**: 31-52, 1926.
3. Hellmer, Hans: Intussusception in Children, Acta Radiol. Suppl. 65, 1948.
4. Sjöstrom, P. M.: Über die unblutige Desinvagination von Darminvaginationsfällen mit Hilfe von Kontrast-einlauf unter Röntgendurchleuchtung, Der Chirurg **6**: 706-714, 1934.
5. Hipsley, P. L.: Acute Intussusception, Brit. M. J. **2**: 717-721, 1935.
6. Dennison, W. W.: Intussusception in Infancy and Childhood, Glasgow M. J. **29**: 71-80, 1948.
7. Ravitch, M. M.: Polypoid Adenomatosis of the Entire Gastrointestinal Tract, Ann. Surg. **128**: 283-298, 1948.
8. Woodhall, B.: Modified Double Enterostomy (Mikulicz) in Radical Surgical Treatment of Intussusception in Children. Arch. Surg. **36**: 989, 1938.
9. Ravitch, M. M., and McCune, R. M.: Reduction of Intussusception by Barium Enema, Ann. Surg. **128**: 904-917, 1948.
10. Ravitch, M. M., and McCune, R. M.: Reduction of Intussusception by Hydrostatic Pressure, Bull. Johns Hopkins Hosp. **82**: 550-568, 1948.

VIRUS HEPATITIS IN INFANCY

ALFRED S. TRAISMAN, M.D., ROBERT C. WHEELER, M.D., AND
DONALD B. FAGER, M.D.
CHICAGO, ILL.

VIRUS HEPATITIS occurring in infants under 18 months of age is rarely encountered. Our knowledge of this disease: its etiology, epidemiology, symptomatology, and pathology; has been widely augmented, especially since 1944, by the work of Lucké, Neefe, Stokes, Mallory, and other workers in this field.[1, 2, 3] Several authors[4, 7] have reviewed the recent literature.

It is frequently stated in pediatric textbooks and in the literature that infectious hepatitis is a rare and mild disease in infants and children. In Mitchell and Nelson's *Textbook of Pediatrics*,[8] it is stated that this condition is "practically nonexistent below the age of 2 years." Randolf and De Vito[9] state that "infectious hepatitis is largely a benign disease, although progression to a diffuse hepatitis, cirrhosis, and death has been reported." Horstmann and associates,[6] reporting on two institutional outbreaks, largely in children, feel that "the disease in children is indeed a mild one." Gellis and Janeway[5] conclude that infectious hepatitis is milder in children than in adults. Recently, Williams and Gaber[10] reported a case of fulminant infectious hepatitis in an infant 2 months old.

Homologous serum hepatitis proceeding to a fatal outcome in this age group is also fortunately an uncommon occurrence. However, since 1943, eight cases of this type have been reported.[7, 11, 14]

During the past fifteen years at The Children's Memorial Hospital, nine cases of virus hepatitis in infants have been recorded. Of these, eight apparently represent infectious hepatitis, four surviving and four having a rapidly fatal outcome. Three patients came to autopsy and are reported here. The ninth patient, presumably suffering from homologous serum hepatitis, died, and is also presented below with post-mortem findings. Three of the four patients reported were seen in the past year and one-half.

CASE REPORTS

CASE 1.—D. T., a 6½-month-old white male infant, was admitted to the hospital with a history of jaundice of two weeks' duration. Three weeks prior to entry, the mother noted that the urine had become a deeper yellow, and one week later that the skin and sclera became jaundiced. The color of the stool was unchanged. Four days before admission he became somewhat irritable. However, his appetite was good and he was not febrile. No history was obtained of any contact with any jaundiced individuals or of any previous transfusions, injections, or immunizations. The mother stated that she was Rh negative and the father Rh positive, but that her three pregnancies had resulted in normal

From The Children's Memorial Hospital and the Otho S. A. Sprague Memorial Institute Laboratory, Chicago, Ill.
Read before the Pediatric Section of the Illinois Medical Society, May 24, 1950.

infants in whom there was no evidence of hemolytic disease. The birth history was normal and his physical development was good. He had had chicken pox at 3 months of age and rubella at 5 months.

Physical examination revealed a well-developed, well-nourished, icteric infant in no distress. The liver was palpable 3.5 cm. below the costal margin. The blood count revealed 2,250,000 red blood cells with 6 Gm. Hb, and 29,800 white blood cells with 81 per cent lymphocytes and 255,000 platelets. Urine analysis showed the presence of bile. A very pale, yellow stool contained only a trace of bile. A cephalin flocculation test was 4 plus. The total proteins were 5.1 Gm. per cent with 2.8 Gm. per cent albumin. Routine blood agglutinations and a heterophile antibody test were negative. The icterus index was 91 units. The qualitative van den Bergh gave strong immediate direct and strong immediate indirect reactions. X-ray of the chest revealed no evidence of pulmonary disease. On the day following admission, his condition unexpectedly began to deteriorate rapidly. He became semistuporous and developed respiratory distress. The liver could no longer be felt. Supportive measures consisted essentially of parenteral glucose, plasma, and blood as well as penicillin, sufadiazine, and vitamin B complex. He expired on the third hospital day.

Necropsy.—Necropsy revealed the body of a well-nourished infant who weighed 8.6 kilograms and measured 79 centimeters in length. The skin and sclera were markedly icteric. There was edema of the eyelids, hands, and feet. On internal examination all the viscera showed a yellowish discoloration. The peritoneal cavity contained 100 c.c. of a clear, dark yellow fluid.

The most significant pathologic findings were in the liver, which weighed 210 grams (normal is 227 grams for this age). Its consistency was moderately reduced and it was flabby in some areas and nodular in others. The anterior margin was moderately sharp and bilobed in appearance. The capsule was not thickened, but the diaphragmatic and undersurfaces were markedly nodular (Figs. 1, 2). Some of these (regenerating) nodules of liver parenchyma measured up to 3 or 4 cm. in diameter. Their consistency was essentially that of normal liver and they appeared greenish-brown in color. The depressed areas between the nodules were softer, flabby in consistency, and dark, purple-red in color. The cut surface (Fig. 3) revealed the nonuniformity of the gross appearance which is so characteristic of the virus form of hepatic necrosis. Discrete, rounded, greenish-brown nodules occurred sporadically in tissues that were markedly congested and gave the appearance of increased lobular markings.

Microscopic sections of the liver were identical to what has been described by Lucké and Mallory as the virus form of hepatic necrosis. In sections from the dark, purple-red areas, the liver cells had disappeared completely (Fig. 4), but the lobules were still outlined by portal triads and proliferating perilobular bile ducts. The disappearance of liver cells caused the portal triads to lie nearer together. The sinusoids in areas of "red atrophy" were often engorged with blood, but their reticulum remained intact. In some of the lobules the reticulum was collapsed and its fibers appeard thickened. The portal and perilobular regions were markedly infiltrated with mononuclear cells. The Kupffer cells were numerous and their cytoplasm contained large amounts of engulfed yellow-brown pigment which appeared to be lipofusein, or so-called "waste pigment." The central veins were only mildly infiltrated with mononuclear cells, but hyalinization of their walls was prominent. In contrast to the areas of "red atrophy" the nodular areas were representative of ischemic regenerative hyperplasia. These portions were composed of atypically formed "lobules" which varied in size and shape. An abundance of new parenchyma had formed by multiplication of cells that,

Fig. 1.

Fig. 2.

Fig. 3.

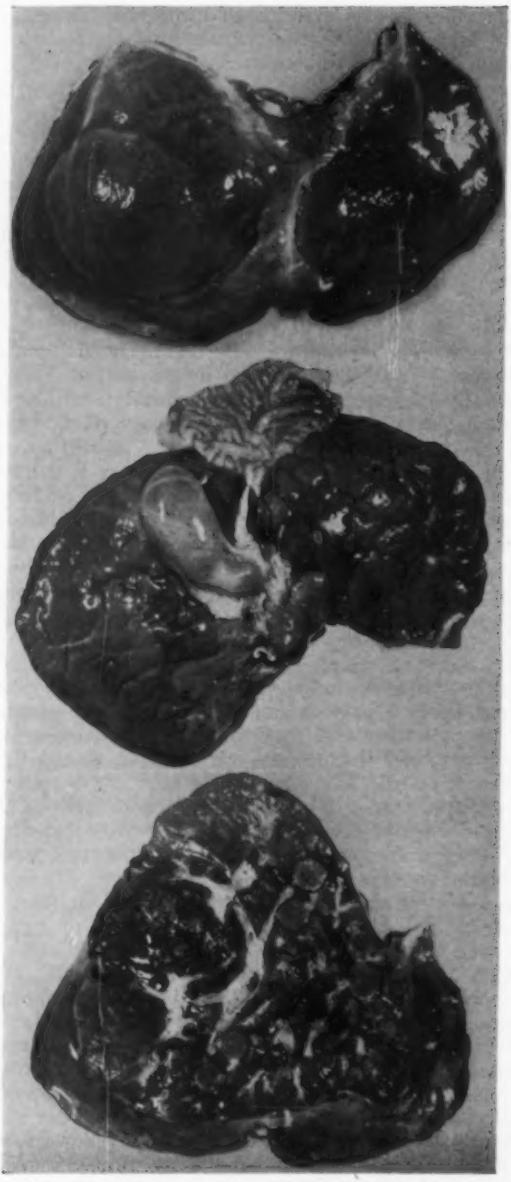


Fig. 1.—Case 1. The diaphragmatic surface of the liver showing large nodules of regenerated parenchyma.

Fig. 2.—Case 1. The hilum surface of the liver showing the nodular areas of regenerated parenchyma and depressed areas of "red atrophy."

Fig. 3.—Case 1. Cut surface of the liver showing discrete nodules of regenerated parenchyma in areas of "red atrophy."

for a time, had escaped destruction. These cells, however, no longer had a healthy appearance, but in most regions of regeneration had undergone secondary degeneration. The prominent nuclei were obviously disintegrating. These tissues showed an increase in polymorphonuclear leucocytes.

Anatomic Diagnosis.—Subacute infectious (virus) hepatic necrosis; jaundice; ascites (100 c.c.); hemorrhagic lesions of the stomach and intestines; splenomegaly with marked congestion and depletion of lymphoid elements; acute glomerulitis; edema of the eyelids, hands, and feet; edema of the brain; foramen magnum compression ring on the cerebellum; hypertrophy of the heart (moderate); bronchopneumonia (slight); and intra-alveolar hemorrhages.

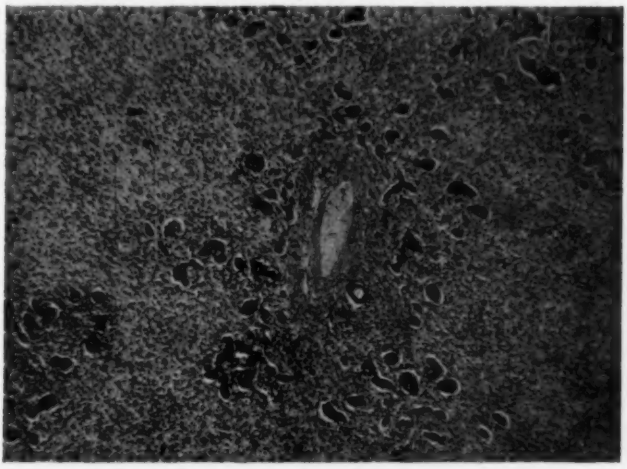


Fig. 4.—Case 1. Photomicrograph showing an area with the entire absence of liver cells. Numerous branching perilobular bile ducts and mononuclear cells are present.

CASE 2.*—M. L. B., a 10-month-old white female infant, was admitted because of a three-week history of progressive jaundice, apathy, anorexia, and increasing enlargement of her abdomen. During this period she vomited on several occasions, her urine had become darker, and her stools clay-colored. No rise in temperature was noted. The birth history was uncomplicated and her general health had been excellent. No contact with persons having jaundice or with hepatotoxic agents was elicited. Three injections of pertussis fluid vaccine and one of diphtheria-tetanus fluid toxoid had been administered during the previous three and one-half months. Autoclaved syringes and needles were used.

Physical examination on admission revealed a small, moderately well-developed and well-nourished infant with rather marked jaundice. The liver was palpable 5 cm. below the costal margin and the abdomen was protuberant. No fluid wave was demonstrated. Moderate generalized lymphadenopathy was present. On admission her blood count contained 4,300,000 red blood cells with 12.5 Gm. Hb, and 11,400 white blood cells per cubic millimeter. The differential count showed 28 per cent polymorphonuclear leucocytes, 71 per cent lymphocytes, and 1 per cent monocytes. There were 218,000 platelets. Bleeding and clotting times were normal. The icterus index was 71 units,

*Reported with a group of cases in "Clinical Conference at the Children's Memorial Hospital of Chicago"—J. Pediat. 35:107, 1949.

cholesterol was 316 mg. per cent and the cephalin flocculation test was 4 plus. The van den Bergh gave immediate direct and indirect reactions. The heterophile antibody titer was in the normal range. Urine analysis demonstrated the presence of bile. Stools varied from brown to clay colored. Bone marrow smear showed normal maturation forms; however, the predominating cell (61 per cent) was considered an abnormal constituent according to our hematologist.

During the hospital stay, the icterus gradually increased. Therapeutic measures consisted essentially of intravenous fluids, blood transfusions, and penicillin. On the seventh day she suddenly became semistuporous, febrile, and began to have respiratory difficulty. The total white count rose to 29,750 with a lymphocytosis of 75 per cent, the majority of which were atypical forms such as have been described in this condition. On the following day she expired.

Necropsy.—Necropsy by Dr. Eugene Slotkowski revealed the body of a normally developed but poorly nourished 10-month-old female infant who weighed 6.6 kilograms and measured 70 centimeters in length. The skin and sclera were moderately icteric. On internal examination all the viscera showed a yellowish discoloration. The peritoneal cavity contained only 5 c.c. of yellowish, clear fluid.

The most significant pathologic findings were in the liver which weighed 344 grams (normal for this age is 274 grams). On gross examination it was noted to be enlarged, reddish-brown in color, and smooth and firm in consistency except for two small areas, one in the right lobe and the other in the left lobe. These were yellow in color and firmer than the remainder of the liver. On cut surface the latter areas were a very light brown, homogeneous, and fairly well demarcated from the surrounding parenchyma. The adjacent tissue was pinkish-brown and the lobulations could not be seen distinctly.

On microscopic examination of the red areas, or the so-called normal-looking portions of the liver, it was noted that the hepatic cells had disappeared completely, but the lobules were still outlined by proliferating perilobular ducts. The sinusoids were greatly engorged with red cells, but their reticulum framework was not destroyed. Throughout the lobules were scattered numerous inflammatory cells and macrophages. As a result of the destructive process, entire lobules throughout large areas of the liver had been reduced to skeletal frames. Any fragment of recognizable hepatic parenchyma that still remained was found in the peripheral zone of the lobules. Throughout the areas of destruction Kupffer cells had engulfed numerous small granules of yellow pigment.

In the nodular yellow areas the parenchyma was in a state of regenerative hyperplasia. New hepatic cells had been formed, but their architectural pattern only rarely approached the normal. They took the form of binucleated or multinucleated cells that appeared to extend from remaining portions of the hepatic cords into the still intact stroma. The marked degree of ischemia of the hyperplastic tissue stood out in contrast to the great engorgement of the tissue in the areas of "red atrophy." About the regenerative "lobules" were numerous proliferating perilobular bile ducts.

Anatomic Diagnosis.—Subacute infectious (virus) hepatic necrosis; jaundice; acites (slight); intestinal hemorrhage; splenomegaly (moderate); enteritis; marked mesenteric lymphadenopathy; petechial hemorrhages in the epicardium; hydrothorax (slight); and mild cervical, axillary, and inguinal adenopathy.

CASE 3.—L. D., a 9-month-old white male infant, was admitted to the hospital in 1934. He had been born at full term after an uncomplicated delivery. The postnatal period was uneventful, and, except for an occasional cold, the past history was uneventful. Two weeks prior to admission he developed an upper-respiratory infection, characterized largely by coryza. Four days before

entry it was noted that his urine became darker and his stools progressively lighter in color. On the following day he developed jaundice. During these four days he was irritable, his appetite diminished and he vomited several times.

Physical examination revealed a well-developed, jaundiced infant with coryza and evidence of rickets. The liver was felt 2 fingerbreadths below the costal margin; the edge was smooth and tender. The spleen tip was palpable. The temperature was normal. The blood count showed 4,500,000 red blood cells, 20,000 white blood cells, and a hemoglobin of 65 per cent, with 57 per cent polymorphonuclear leucocytes, 39 per cent lymphocytes, and 4 per cent monocytes. The urine contained 4-plus bile. The van den Bergh gave a biphasic reaction and the icterus index was 40 units. An x-ray of the chest was normal.

On the day after admission the patient's temperature began to rise, vomiting became persistent, and several convulsions occurred. Numerous coarse râles were heard in the chest. He expired on the second hospital day.

Necropsy.—Necropsy by Dr. Allan Roos revealed the body of a well-nourished, jaundiced infant. Fresh clotted blood was found in the mouth, but no points of local bleeding were apparent. On internal examination all the viscera showed a yellowish discoloration.

The most significant pathologic findings were in the liver which weighed 130 grams (normal for this age is 240 grams). Its anterior margin extended to 1 cm. above the costal margin. The capsule was smooth and the parenchyma appeared a blotchy yellow and brown. On cut surface the hepatic lobules were indistinct in many places. However, in other regions the periportal areas were dark brown in contrast to the yellowish parenchyma found elsewhere.

Microscopic sections were similar in some respects to those already described in Case 1. There were wide areas of hepatic cell destruction with the loss of normal histologic architecture. Numerous proliferating bile ducts were present. In contrast to Case 1, special stains revealed an abundance of fat to be present throughout most of the liver, but most abundant in the periportal spaces. The cytoplasm of many liver cells was replaced with varying-sized fat vacuoles. The liver cells were no longer in cords but were scattered throughout their "lobules." The cellular reaction was quite marked but no particular cell type predominated.

Anatomic Diagnosis.—Early acute infectious (virus) hepatic necrosis; jaundice; subpleural hemorrhages in the lungs; confluent lobular pneumonia (moderate); and pulmonary atelectasis.

CASE 4.—R. T. was brought to the hospital at the age of 2½ months. The mother was unable to give a reliable or detailed history. He was born at full term and delivered by cesarean section. Ten days prior to admission he presumably developed an upper-respiratory infection and a diarrhea on the day of entry. When first seen his temperature was 106° F., and he was malnourished and extremely dehydrated. His breathing was rapid and he was having frequent, watery stools. Except for spasticity in all extremities, the rest of the physical examination was essentially negative. The immediate therapy consisted chiefly of what was thought to be irradiated human serum, penicillin, and streptomycin. During convalescence he began to have major convulsions which were persistent and recurred over a period of five days. Developmental retardation was evident upon recovery.

At the age of 8 months he was readmitted with a history of yellow sclera, dark urine, and an increase in the size of the abdomen which had been noted during the previous five days. His appetite had been satisfactory, his stools were normal, and no fever had been noted. There was no history of any contact with jaundiced individuals. On examination the skin and sclera were slightly

icteric. He showed a generalized, moderate lymphadenopathy, the liver was enlarged 4 cm. below the costal margin, the spleen was felt 3 cm. below the costal margin, and continued evidence of a spastic quadreplegia was apparent.

The blood count revealed 3,160,000 red blood cells, a hemoglobin of 8.2 Gm., and 6,000 white blood cells with 66 per cent lymphocytes, 30 per cent polymorphonuclear cells, and 3 per cent monocytes. There were only 30,000 platelets per cubic millimeter. The urine was positive for bile. A van den

Fig. 5.

Fig. 6.

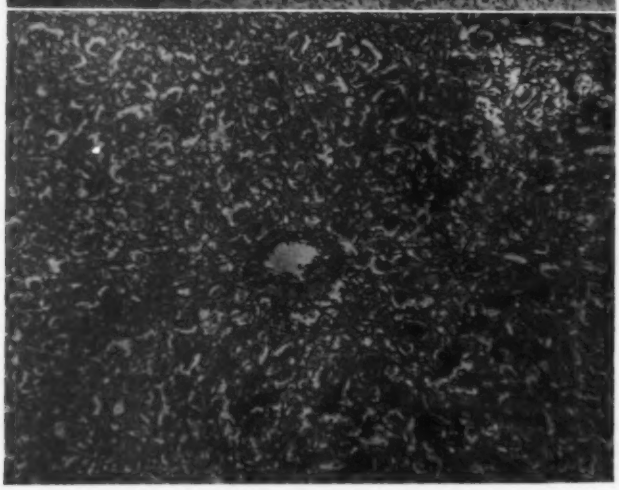


Fig. 5.—Case 4. A central vein cut obliquely showing infiltration with mononuclear cells, hyalinization and thickening of its wall. Multinucleated regenerating liver cells are scattered throughout the lobule.

Fig. 6.—Case 4. Photomicrograph showing a central vein of a regenerating lobule with intact reticulum. (Reticulum stain.)

Bergh test gave immediate positive direct and indirect reactions. The icterus index on admission was 42 units and the total protein was 4.7 Gm. per cent with 2.9 Gm. per cent albumin. A cephalin flocculation test was 4 plus and the alkaline phosphatase was 10.9 units. The stool contained 360 mg. of urobilinogen per 100 Gm. The bone marrow was normal.

He was given a high-protein, high-carbohydrate diet with vitamin supplements and later on received parenteral Amigen and 5 per cent glucose in water. The course was rapidly downhill. The jaundice progressively deepened, the liver receded under the costal margin, and on the fourteenth hospital day the infant expired. The clinical diagnosis was homologous serum hepatitis, resulting from serum he received 151 days prior to the onset of the illness.

Necropsy.—Necropsy revealed the body of a poorly-nourished infant who weighed 5.4 kilograms and measured 66 centimeters in length. The skin and sclera were moderately icteric. The suboccipital and cervical lymph nodes were enlarged, shotty, and discrete. On internal examination all the viscera showed a yellowish discoloration. The peritoneal cavity contained 1,000 c.c. of a dark yellow, clear fluid.

The most significant pathologic findings were in the liver which weighed 184 grams (normal for this age is 260 grams). Its consistency was markedly reduced and it was flabby to palpation, especially the left lobe. The anterior margin was sharp and bilobed in appearance. The capsule was not thickened, but the liver substance was uniformly finely nodular. The marked congestion of the cut surface gave it an increased lobular appearance.

Microscopic sections were again identical to what has been described as the virus form of hepatic necrosis.[1, 3] Sections were similar in many respects to those already described in Case 1 (Fig. 4). However, the regenerative regions of the parenchyma showed evidence of having been present for a shorter time. Wide areas of ischemic regenerative hyperplasia were not found. In contrast, cells were not arranged in columns, but lay isolated or in small groups within the intact stroma. Such cells formed syncytium in disorderly groups (Figs. 5, 6). The walls of many of the central lobular veins were moderately infiltrated with mononuclear cells and hyalinization and thickening was more prominent than in Case 1.

Anatomic Diagnosis.—Subacute homologous serum (virus) hepatic necrosis; jaundice; ascites; acute myocarditis (slight); splenomegaly with marked congestion and depletion of lymphoid elements; focal interstitial nephritis; malnutrition; serous atrophy of fat; edema of the lungs; intra-alveolar hemorrhages in the lungs; hydrocele (right side); generalized lymphadenopathy; and solitary petechial hemorrhage in the cerebellum.

DISCUSSION

From the cases reported above it appears that virus hepatitis, while uncommon in the infant age group, is not to be regarded as a mild disease with a good prognosis. Rather, it is to be viewed as an extremely grave and serious condition.

Little has been written of virus hepatitis in infants because it occurs so rarely and only a very few cases have been reported in the literature. Much has been written, however, about this disease in older children where it does seem to be relatively benign.

The case of homologous serum hepatitis seems to support the contention of Moloshok and associates[7] that the prognosis of this condition is worse in infants.

Jaundice and hepatomegaly were constant findings. In three patients the enlarged livers became smaller terminally. Two showed splenomegaly, and in two a moderate, but not unusual, generalized adenopathy was noted. In contrast to adults where a leucopenia is a common finding, three of our patients with infectious hepatitis had a leucocytosis, two of these showing a marked lymphocytosis.

The sudden occurrence of liver failure in the first patient, who had previously tolerated his infection seemingly well, illustrates the necessity of a guarded prognosis until complete recovery takes place.

Death occurred in each from one to four weeks after the onset of signs and symptoms of their illness.

Necropsy in all cases showed the typical pathologic findings of virus hepatic necrosis.

SUMMARY

1. In the past fifteen years, nine cases of virus hepatitis in infancy have been seen and studied at The Children's Memorial Hospital. Five of these (56 per cent) had a fatal outcome.

2. Four infants who came to autopsy are presented in detail with the clinical, laboratory, and post-mortem findings.

3. Contrary to general belief, our experience suggests that although this condition is rare in infancy, the prognosis is much more serious than in older children.

REFERENCES

1. Lucké, B.: The Pathology of Fatal Epidemic Hepatitis, Am. J. Path. 20: 471, 1944.
2. Neefe, J. R., and Stokes, J., Jr.: Epidemic of Infectious Hepatitis, J. A. M. A. 128: 1063, 1945.
3. Lucké, B., and Mallory, T.: The Fulminant Form of Epidemic Hepatitis, Am. J. Path. 22: 867, 1946.
4. Havens, W. P., Jr.: Infectious Hepatitis, Medicine 27: 279, 1948.
5. Gellis, S. S., and Janeway, C. A.: Viral Hepatitis, New England J. Med. 239: 503, 1948.
6. Horstmann, D. M., Havens, W. P., and Deutsch, J.: Infectious Hepatitis in Childhood, J. PEDIAT. 30: 381, 1947.
7. Moloshok, R. F., Karelitz, S., and Strauss, L.: Homologous Serum Hepatitis in Infants and Children, Pediatrics 3: 651, 1949.
8. Nelson, Waldo E., editor: Textbook of Pediatrics (Mitchell-Nelson), ed. 4, Philadelphia, 1946, W. B. Saunders Company.
9. Randolf, M., and De Vito, A.: Infectious Hepatitis: A Review of Thirty-two Cases in Children's Hospital, Clin. Proc. Children's Hospital, Washington, D. C. 3: 242, 1947.
10. Williams, R. R., and Gaber, B.: The Fulminant Form of Epidemic Hepatitis in a Two-Month-Old Infant, J. PEDIAT. 35: 244, 1949.
11. Ministry of Public Health: Homologous Serum Jaundice, Lancet 1: 83, 1943.
12. Wood, D. A., and Black, M. B.: Further Notes on the Pathology of Acute Epidemic Hepatitis and Homologous Serum Jaundice, Am. J. Clin. Path. 16: 746, 1946.
13. Bruyn, H. B.: Homologous Serum Hepatitis Following Transfusion in an Infant, J. PEDIAT. 31: 60, 1947.
14. Schmidt, E. C. H., and Lee, C. H.: Fatal Homologous Serum Hepatitis in a Young Infant, J. PEDIAT. 34: 226, 1949.

BODY SIZE NORMS FOR CHILDREN FOUR TO EIGHT YEARS OF AGE

HOWARD V. MEREDITH, PH.D.
EUGENE, ORE.

IT HAS become a medical commonplace that biologic research and clinical practice each render useful services to the other. This article presents some research results on the body size of well-nurtured, nonpathologic, white children, which I have assembled in convenient form for use by pediatricians and school physicians.

Prefatory reference is appropriate to certain other norms for body size. Many clinicians currently are employing the Vickers and Stuart[1] tables or the Stuart and Meredith[2] charts. The norms afforded by my report do not replace these; they complement them. Vickers and Stuart, for instance, supply norms for four body measurements not treated in this article (head circumference, chest breadth, stature, and body weight); this report, in turn, provides norms for several measurements not dealt with by Vickers and Stuart (abdomen girth, shoulder width, length, and circumference of the extremities).

Some may find their normative needs with reference to body size adequately filled by the tables of this article except for the fact that the tables do not include body weight or stature. The attention of these persons is called to a recent article by this writer[3] which furnishes norms for stature and weight obtained by the same statistical procedure as is utilized in the present report.

Whenever norms are presented for practical use, the practitioner needs to know how they were obtained. The intelligent use of any biologic "frame of reference" presupposes a sound functional knowledge regarding the subjects and methods employed in its derivation.

The subjects from whom the norms of this paper were obtained were children four to eight years of age enrolled between 1940 and 1949* in the University of Iowa experimental preschool laboratory and elementary school. All were physically normal boys and girls of northwest European ancestry and of the professional or managerial socioeconomic groups. The environmental conditions with reference to nutrition and health care were generally superior, in almost all instances the children had been under continuous pediatric guidance from birth. It follows, then, that our subjects represent the type of adequately cared-for children pediatricians and school physicians prefer to have utilized in the construction of norms for growth appraisal.

All of the anthropometric examinations were made within one week of each child's birthday. Consequently, the norms for "4 years" are based exclusively on children measured at or very near this postnatal age, the norms

From the School of Health and Physical Education, University of Oregon, and the Iowa Child Welfare Research Station, University of Iowa. The author supervised collection of the data for this study while at the University of Iowa and prepared the data for publication after transferring to the University of Oregon.

*The inappropriateness of evaluating present-day children with norms based upon data collected more than a decade or so ago has been clearly shown.[4, 5]

for "5 years" on children at or very near this postnatal age, and so forth. The number of children examined at each age is as follows:

Age (yr.)	4	5	6	7	8
Males	105	130	122	116	102
Females	98	121	113	102	87

As will be seen from Tables I and II, normative values by sex and age were obtained for nine body dimensions—four of the trunk (chest girth, abdomen

TABLE I. CHILDHOOD NORMS FOR NINE MEASUREMENTS OF BODY SIZE IN BOYS

(CENTIMETERS):		SMALL	MODERATELY SMALL	AVERAGE	MODERATELY LARGE	LARGE
			4 years			
Girth:	Chest	<51.0	51.0-52.2	52.3-54.7	54.8-56.4	>56.4
	Abdomen	<49.7	49.7-51.9	52.0-54.9	55.0-57.5	>57.5
	Arm	<15.8	15.8-16.4	16.5-17.8	17.9-19.1	>19.1
	Leg	<20.5	20.5-21.1	21.2-22.9	23.0-24.0	>24.0
Width:	Shoulders	<22.2	22.2-22.9	23.0-24.1	24.2-24.9	>24.9
	Hips	<16.1	16.1-16.8	16.9-17.8	17.9-18.5	>18.5
Length:	Stem	<56.7	56.7-58.9	59.0-61.3	61.4-62.9	>62.9
	Upper limb	<41.2	41.2-42.7	42.8-45.1	45.2-46.8	>46.8
	Lower limb	<41.6	41.6-43.1	43.2-45.5	45.6-47.1	>47.1
			5 years			
Girth:	Chest	<52.1	52.1-53.5	53.6-56.3	56.4-58.2	>58.2
	Abdomen	<50.9	50.9-53.1	53.2-56.4	56.5-59.1	>59.1
	Arm	<16.1	16.1-16.8	16.9-18.3	18.4-19.7	>19.7
	Leg	<21.3	21.3-22.0	22.1-23.9	24.0-25.2	>25.2
Width:	Shoulders	<23.4	23.4-24.1	24.2-25.4	25.5-26.2	>26.2
	Hips	<16.9	16.9-17.6	17.7-18.7	18.8-19.4	>19.4
Length:	Stem	<59.2	59.2-61.5	61.6-64.0	64.1-65.7	>65.7
	Upper limb	<43.8	43.8-45.6	45.7-48.1	48.2-49.8	>49.8
	Lower limb	<45.2	45.2-47.2	47.3-49.9	50.0-51.6	>51.6
			6 years			
Girth:	Chest	<53.5	53.5-55.0	55.1-58.0	58.1-60.4	>60.4
	Abdomen	<52.1	52.1-54.2	54.3-57.9	58.0-60.9	>60.9
	Arm	<16.5	16.5-17.3	17.4-18.9	19.0-20.4	>20.4
	Leg	<22.2	22.2-23.0	23.1-25.0	25.1-26.6	>26.6
Width:	Shoulders	<24.6	24.6-25.3	25.4-26.7	26.8-27.6	>27.6
	Hips	<17.7	17.7-18.4	18.5-19.6	19.7-20.3	>20.3
Length:	Stem	<61.7	61.7-64.2	64.3-66.7	66.8-68.6	>68.6
	Upper limb	<46.6	46.6-48.6	48.7-51.2	51.3-52.8	>52.8
	Lower limb	<48.9	48.9-51.2	51.3-54.2	54.3-56.1	>56.1
			7 years			
Girth:	Chest	<55.0	55.0-56.5	56.6-60.0	60.1-62.8	>62.8
	Abdomen	<53.4	53.4-55.4	55.5-59.4	59.5-62.7	>62.7
	Arm	<16.8	16.8-17.7	17.8-19.4	19.5-21.0	>21.0
	Leg	<23.1	23.1-24.0	24.1-26.1	26.2-28.0	>28.0
Width:	Shoulders	<25.8	25.8-26.5	26.6-28.0	28.1-28.9	>28.9
	Hips	<18.5	18.5-19.2	19.3-20.4	20.5-21.2	>21.2
Length:	Stem	<64.1	64.1-66.7	66.8-69.3	69.4-71.4	>71.4
	Upper limb	<49.5	49.5-51.7	51.8-54.2	54.3-56.0	>56.0
	Lower limb	<52.6	52.6-55.3	55.4-58.5	58.6-60.5	>60.5
			8 years			
Girth:	Chest	<56.9	56.9-58.3	58.4-62.1	62.2-65.4	>65.4
	Abdomen	<54.7	54.7-56.6	56.7-60.9	61.0-64.4	>64.4
	Arm	<17.2	17.2-18.2	18.3-20.0	20.1-21.7	>21.7
	Leg	<24.1	24.1-25.0	25.1-27.2	27.3-29.4	>29.4
Width:	Shoulders	<26.9	26.9-27.6	27.7-29.1	29.2-30.1	>30.1
	Hips	<19.2	19.2-19.9	20.0-21.2	21.3-22.1	>22.1
Length:	Stem	<66.5	66.5-69.0	69.1-71.7	71.8-73.9	>73.9
	Upper limb	<52.4	52.4-54.6	54.7-57.2	57.3-59.2	>59.2
	Lower limb	<56.1	56.1-59.1	59.2-62.4	62.5-64.5	>64.5

girth, shoulder width, hip width), four of the extremities (arm girth, leg girth, length of the upper limb, length of the lower limb), and one over-all dimension of the head, neck, and trunk (stem length). One dimension, upper limb length, was not determined on all of the children in the study, i.e., the number of children measured in each age-sex group was 10 to 20 less for upper limb length than for the other measures.

TABLE II. CHILDHOOD NORMS FOR NINE MEASUREMENTS OF BODY SIZE IN GIRLS

(CENTIMETERS):		SMALL	MODERATELY SMALL	AVERAGE	MODERATELY LARGE	LARGE
			4 years			
Girth:	Chest	<48.9	48.9-50.4	50.5-52.6	52.7-54.4	>54.4
	Abdomen	<48.8	48.8-51.0	51.1-53.8	53.9-56.9	>56.9
	Arm	<15.4	15.4-16.2	16.3-17.4	17.5-18.6	>18.6
	Leg	<20.1	20.1-21.1	21.2-22.6	22.7-23.7	>23.7
Width:	Shoulders	<21.9	21.9-22.6	22.7-23.7	23.8-24.5	>24.5
	Hips	<15.9	15.9-16.5	16.6-17.4	17.5-18.2	>18.2
Length:	Stem	<56.2	56.2-57.9	58.0-60.2	60.3-61.7	>61.7
	Upper limb	<41.0	41.0-41.9	42.0-43.9	44.0-45.1	>45.1
	Lower limb	<41.5	41.5-42.8	42.9-44.8	44.9-46.4	>46.4
			5 years			
Girth:	Chest	<50.1	50.1-51.6	51.7-54.1	54.2-56.2	>56.2
	Abdomen	<50.1	50.1-52.3	52.4-55.3	55.4-58.5	>58.5
	Arm	<15.7	15.7-16.6	16.7-17.9	18.0-19.2	>19.2
	Leg	<20.9	20.9-22.1	22.2-23.7	23.8-24.9	>24.9
Width:	Shoulders	<23.1	23.1-23.8	23.9-25.0	25.1-25.8	>25.8
	Hips	<16.7	16.7-17.3	17.4-18.3	18.4-19.1	>19.1
Length:	Stem	<58.7	58.7-60.5	60.6-62.8	62.9-64.4	>64.4
	Upper limb	<43.6	43.6-44.8	44.9-46.9	47.0-48.1	>48.1
	Lower limb	<45.1	45.1-46.9	47.0-49.2	49.3-50.9	>50.9
			6 years			
Girth:	Chest	<51.5	51.5-53.0	53.1-55.8	55.9-58.3	>58.3
	Abdomen	<51.3	51.3-53.5	53.6-56.7	56.8-60.4	>60.4
	Arm	<16.1	16.1-17.1	17.2-18.6	18.7-19.9	>19.9
	Leg	<21.8	21.8-23.1	23.2-24.8	24.9-26.2	>26.2
Width:	Shoulders	<24.3	24.3-25.0	25.1-26.3	26.4-27.2	>27.2
	Hips	<17.5	17.5-18.1	18.2-19.2	19.3-20.0	>20.0
Length:	Stem	<61.3	61.3-63.2	63.3-65.4	65.5-67.1	>67.1
	Upper limb	<46.4	46.4-47.8	47.9-50.0	50.1-51.2	>51.2
	Lower limb	<48.8	48.8-50.8	50.9-53.5	53.6-55.4	>55.4
			7 years			
Girth:	Chest	<53.0	53.0-54.5	54.6-57.6	57.7-60.6	>60.6
	Abdomen	<52.7	52.7-54.8	54.9-58.4	58.5-62.3	>62.3
	Arm	<16.5	16.5-17.5	17.6-19.2	19.3-20.5	>20.5
	Leg	<22.7	22.7-24.2	24.3-25.9	26.0-27.7	>27.7
Width:	Shoulders	<25.5	25.5-26.2	26.3-27.6	27.7-28.5	>28.5
	Hips	<18.3	18.3-18.9	19.0-20.1	20.2-20.9	>20.9
Length:	Stem	<63.8	63.8-65.7	65.8-68.0	68.1-69.9	>69.9
	Upper limb	<49.5	49.5-50.7	50.8-53.1	53.2-54.4	>54.4
	Lower limb	<52.6	52.6-54.9	55.0-57.7	57.8-59.8	>59.8
			8 years			
Girth:	Chest	<54.9	54.9-56.4	56.5-59.9	60.0-63.2	>63.2
	Abdomen	<54.1	54.1-56.1	56.2-60.1	60.2-64.0	>64.0
	Arm	<16.9	16.9-18.0	18.1-19.9	20.0-21.2	>21.2
	Leg	<23.7	23.7-25.3	25.4-27.1	27.2-29.1	>29.1
Width:	Shoulders	<26.6	26.6-27.3	27.4-28.7	28.8-29.7	>29.7
	Hips	<19.1	19.1-19.7	19.8-21.0	21.1-21.8	>21.8
Length:	Stem	<66.2	66.2-68.1	68.2-70.5	70.6-72.3	>72.3
	Upper limb	<52.2	52.2-53.6	53.7-56.1	56.2-57.4	>57.4
	Lower limb	<56.3	56.3-58.7	58.8-61.7	61.8-63.8	>63.8

The nine measures are defined below in a manner as succinct as appears compatible with their clear characterization.

Chest Girth.—The instrument used in taking all of the girth measurements was a steel millimeter tape. Chest girth was determined as the circumference of the trunk at the level of the xiphisternal junction. In preparation for measurement each child stood in a natural manner with head erect and with the upper extremities relaxed and held slightly away from the sides of the body. The tape was passed around the thorax in a horizontal plane at the xiphisternal level and brought into light contact with the skin. The reading made was the median girth during normal respiration.

Abdomen Girth.—Wherever possible, this was determined as the circumference of the trunk at the level of the umbilicus. In children showing umbilical protrusion, the tape rested against the perimeter of the abdomen at a level immediately above the umbilicus. The posture of the child, the tension applied to the tape, and the attempt to obtain a midrespiration record were all the same as for chest girth.

Arm Girth.—The measurements of arm girth, length of upper limb, and leg girth were taken on the left side. For measurement of arm girth the child stood in a natural manner with the upper extremities hanging in a relaxed condition at the sides of the body and with the left extremity slightly abducted so that the arm was not in contact with the lateral wall of the thorax. The tape was passed around the arm approximately halfway between the shoulder and the elbow. This area was explored to find the greatest girth at right angles to the long axis of the limb and inferior to any surface indication of the deltoid muscle. The reading was taken with the tape in sufficiently light contact with the skin to avoid compression of the tissues.

Leg Girth.—The child stood with his feet about 6 inches apart and his weight distributed equally through both lower limbs. Maximum circumference of the left leg was determined by passing the tape around the leg in the region of the calf and exploring to find the largest reading at right angles to its long axis. As for arm girth, the tape was read at "light contact" tension.

Shoulder Width.—Sliding metal calipers having broad flat aluminum branches were used in taking this and the succeeding measurement. The shoulder breadth obtained was biacromial diameter. Each child stood with upper extremities extended downward and the shoulders neither "slumped forward" nor "thrown back." Moderate pressure was applied to the caliper branches in order to have the record approximate the skeletal distance between the most lateral points of the acromion processes.

Hip Width.—This measurement was determined as the distance between the lateralmost point of the crest of the right ilium and the corresponding landmark for the left ilium, i.e., as bi-iliocristal diameter. After each branch of the calipers had been brought squarely in contact with one of the landmarks, heavy pressure was used in order to approach maximum compression of the overlying soft tissues. In the event the child turned his hips as the pressure was applied, the measurement was retaken.

Stem Length.—The child sat erect on a horizontal bench with his ankles crossed and his knees spread apart. His lower and upper back made contact with an upright board to which a millimeter scale was attached. Stem length was determined as the distance from the surface of the bench to the vertex (the highest point of the head when the head is oriented with the tragion-orbitale plane at right angles to the long axis of the trunk). It follows that stem length is synonomous with vertex-rump length or erect sitting height.

Upper Limb Length.—This measurement was made with wooden sliding calipers and, as previously mentioned, was taken on the left extremity. After extending the extremity at the side of the body and rotating the hand so that its palmar surface faced the lateral surface of the thigh, the distance was found from the most lateral point of the acromion process to the most distal point of the middle finger. The instrument was applied from the rear, care being taken to keep its shaft parallel with the long axis of the limb and to guard against the tendency of many children to tilt the shoulder axis as the limb is extended.

Lower Limb Length.—This measurement was derived by subtraction of each child's stem length from his stature. Stature was measured erect as the distance from soles to vertex with the child oriented against the same anthropometric board used in taking stem length. The child stood with feet almost together; plantar surfaces of heels in firm contact with the floor; and heels, buttocks, upper part of back, and rear of head in contact with the board.

All of the measurements were taken on the nude body and obtained with exceptional care. For every child, two anthropometrists each secured a separate series of records. In instances where their results failed to show close agreement, additional measurements were made. Such research rigor affords the clinician ample assurance that the norms were developed with highly reliable data.

Table I has the norms for boys and Table II those for girls. How were these norms constructed? In other words, what procedures were followed in establishing the five normative categories: small, moderately small, average, moderately large, and large?

First, the data were separated according to age, sex, and body dimension, i.e., the 105 measurements of chest girth on 4-year-old boys were placed in one group, the 105 measurements of abdomen girth on 4-year-old boys in a second group, and so forth. Next, each group of measurements was arranged in order (from the lowest value to the highest) and the 10th, 30th, 70th, and 90th percentiles determined. Finally, in a manner analogous to that in which four embryonic slits establish five digits on each hand and foot, these four percentiles were used to delimit the five body size categories.

The 30th and 70th percentiles were used as the limiting values for the normative category designated "average," the 10th percentile as the lower limit of the "moderately small" category, and the 90th percentile as the upper limit of the "moderately large" category. This means that the lowest 10 per cent of each series of measurement values (e.g., the series of chest girth values on the 105 4-year-old boys) define the "small" category, the next 20 per cent the "moderately small" category, the middle 40 per cent the "average" category, the next 20 per cent the "moderately large" category, and the highest 10 per cent the "large" category.

The foregoing description of the source and nature of the norms—of how, when, and on whom the basic data were collected and by what statistical procedures the normative categories were delimited—has laid the necessary foundation for a sound working understanding of their use and interpretation. This working understanding possibly can be made more concrete through a few illustrations.

1. Child N., a boy 5 years of age, is measured in accordance with the methods described in this paper and found to have the following body dimensions: chest girth 60.3 cm., arm girth 21.8 cm., shoulder width 27.5 cm., stem length 67.4 cm., and lower limb length 53.9 cm. Reference to Table I shows this child to fall consistently in the "large" category, i.e., in each aspect of body size measured he ranks among the largest 10 per cent of well-cared-for United States white boys of northwest European ancestry.

2. Body dimensions for Child O., a girl 6 years of age, are: chest girth 54.6 cm., leg girth 24.0 cm., hip width 18.7 cm., stem length 59.8 cm., and lower limb length 47.2 cm. Reference to Table II shows the chest girth, leg girth, and hip width values to be "average" and the stem length and lower limb length values to be "small" It follows that in terms of the norms this child is short in stature and of stocky build.

3. Child R., a girl 7 years of age, is found to measure 17.0 cm. in arm girth, 23.4 cm. in leg girth, 53.9 cm. in upper limb length, and 58.8 cm. in lower limb length. According to Table II this girl has "moderately large" limb lengths and "moderately small" limb girths. Specifically, while over 70 per cent of well-cared-for white girls have shorter limbs less than 30 per cent have limbs of smaller girth. What are the implications? This is a child who warrants careful study to determine whether the norms are registering a healthy slenderness of build or an undesirable state of health arising from some disease condition, nutritional need, or activity deficiency.

4. Measurements for Child M., a boy 8 years of age, are: chest girth 60.5 cm., abdomen girth 67.0 cm., stem length 70.4 cm., upper limb length 51.8 cm., and lower limb length 55.2 cm. According to Table I the child is "average" in chest girth and stem length, "large" in abdomen girth, and "small" in length of the upper and lower limbs. The shortness of limbs in relation to stem, and predominance of abdomen over thorax, may merit thorough pediatric appraisal with reference to the advisability of attempting acceleration of development through a glandular or alternative treatment program.

5. This last example is taken to indicate the usefulness of the norms in progress evaluation. Assume that Child S., a boy, has been examined at 4, 5, and 6 years of age and found to be "average" at each of these ages in all four girths. At 6 years of age his specific records were chest girth 56.0 cm., abdomen girth 54.9 cm., arm girth 17.8 cm., and leg girth 23.7 cm. Now, at age 7 years, his girths are found to be 61.2 cm. for chest, 62.5 cm. for abdomen, 20.9 cm. for arm, and 27.8 cm. for leg, so that in each instance he has shifted into the "moderately large" category. Having brought these growth facts to the attention of the medical clinician, the norms have discharged their function. It is for the school physician or pediatrician to determine what the facts imply, e.g., to discover whether they reflect a healthy trend towards greater stockiness of build or, perchance, a drift toward obesity which may be counteracted in its early stages by competent psychologic and dietary guidance.[6]

SUMMARY

Norms are presented for nine measurements of external body size. They cover the age period from 4 to 8 years for each sex. Description is given of the

subjects, the anthropometric procedures, and the method of norm construction. Illustrations indicate different uses of the norms.

REFERENCES

1. Vickers, V. S., and Stuart, H. C.: Anthropometry in the Pediatrician's Office, J. PEDIAT. 22: 155, 1943.
2. Stuart, H. C., and Meredith, H. V.: Use of Body Measurements in the School Health Program Am. J. Pub. Health 36: 1365, 1946.
3. Meredith, H. V.: A Physical Growth Record for Use in Elementary and High Schools, Am. J. Pub. Health 39: 878, 1949.
4. Meredith, H. V.: The Stature and Weight of United States Children as Influenced by Racial, Regional, Socioeconomic, and Secular Factors, Am. J. Dis. Child. 62: 909, 1941. See also, Meredith, H. V.: Height and Weight of Private School Children in Three Successive Decades, School and Soc. 70: 72, 1949.
5. Meredith, H. V., and Meredith, E. M.: The Stature of Toronto Children Half a Century Ago and Today, Human Biol. 16: 126, 1944.
6. Angel, J. L.: Constitution in Female Obesity, Am. J. Phys. Anthropol. n.s. 7: 433, 1949.

TREATMENT OF HYDROCEPHALUS BY VENTRICULOMASTOIDOSTOMY

WILLIAM A. NOSIK, M.D.
CLEVELAND, OHIO

IN AN historical review of the subject twenty-one years ago, Davidoff,[1] summarized a number of the procedures employed in the treatment of hydrocephalus over the previous forty years. A surprisingly large number of approaches to this problem had been made, a mute testimonial to the general ineffectiveness of the methods used. Except for the subtotal choroid plexectomy few of these procedures have enjoyed any degree of acceptance by those faced with the care of these patients. The plexectomy in itself seems ineffective when the fluid resorption is more seriously impaired.

Various operations have been devised to provide a continuous drainage of the ventricles. From direct external ventricular drainage (after puncture of the fontanels, the cribiform area of the nose, or the orbits), to the internal drainage of the fluid into the subcutaneous and subarachnoid spaces (some twenty-six different procedures), the thought was the same, i.e., to eliminate the fluid or to offer a new absorption area. Attempts were unsuccessfully made to drain the fluid into the sagittal sinus, the jugular, and the superficial temporal veins.[2] Continuous drainage of the cerebrospinal fluid into the peritoneal cavity, the pleural cavity, the thoracic duct,[3] and the urinary bladder via the ureter, have likewise met with failure. A modified uretero-arachnoid anastamosis was recently reported to be effective six months after operation.[4]

In view of the previously mentioned trials and tribulations encountered by others, it is with some trepidation that a continuous ventricular drainage by way of a hitherto unused route is presented here.

This procedure which I term ventriculomastoidostomy, was first performed in March, 1947. The purpose of the operation is to establish a fluid pathway from the temporal horn of the lateral ventricle into the antrum of the mastoid. This is accomplished by connecting the two structures with a section of polyethylene tubing to which a tantalum tip has been attached, the plastic tubing being inserted into the lateral ventricle and the tantalum tip into the antrum. (Fig. 1.) The flow of cerebrospinal fluid progresses from the lateral ventricle into the antrum of the mastoid, through the atrium and the middle ear, down the eustachian tube to the nasopharynx. The details of the surgical technique have been described in a previous publication.[5]

The existence of an open channel from the nasopharynx to the ventricle is an undesirable potential hazard. How great a hazard is presented is not yet apparent since the experience includes only nine patients whose survival times range from several months to the three years presented here. In this group only one patient developed meningitis (one month postoperatively), even though

a satisfactory drainage had not been established. Mild clinical signs and a cellular response in the cerebrospinal fluid were noted, though no organisms were cultured. From the limited experience cited, it is believed that the existence of a higher intracranial pressure forcing the fluid down a narrow tube (1 mm.), as well as the outward beat of the eustachian tube cilia results in a unidirectional flow of fluid into the nasopharynx. It is believed that the constant outward flow of fluid decreases the existing hazard of retrograde infection.

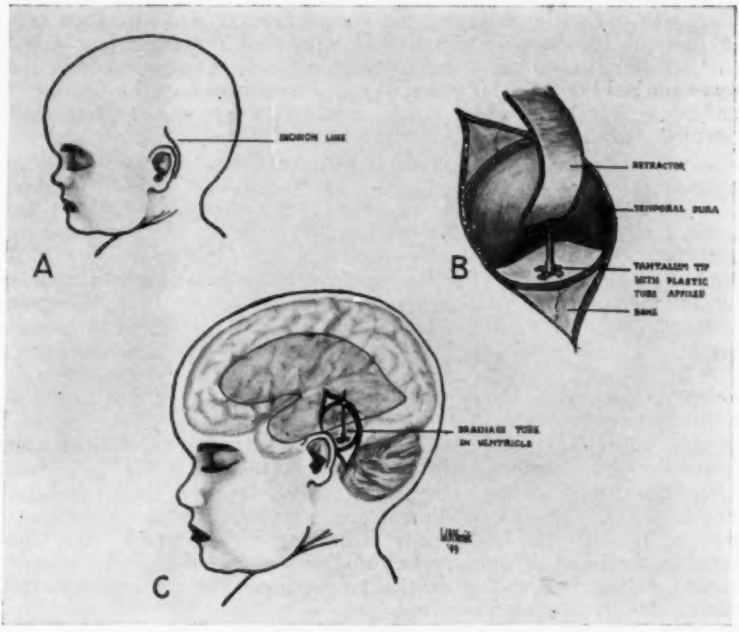


Fig. 1.—Description of the operative procedure. *A*, Position of incision line. *B*. Close-up of the operative site. *C*. Schematic representation of the drainage tube in position, connecting ventricle and antrum. (Reprinted from the *Journal of Neurosurgery*.)

The relative simplicity of the operation, when compared to other operations for the control of hydrocephalus, favored its usage in patients whose physical condition would not allow a bilateral plexectomy or an operation designed to circumvent an obstruction. It is of academic interest only to determine whether the hydrocephalus under consideration is of obstructive or nonobstructive type and makes unnecessary those determinations in the poor risk patient.

There is presented here the case report of a patient who had undergone ventriculomastoidostomy three years before. The patient was considered an extremely poor risk for any other major surgical treatment to relieve the hydrocephalus. While she was not regarded as an ideal candidate for this procedure, the operation was performed and the result noted here.

CASE REPORT

The parents of L. J. C., our patient, gave as chief complaint on admittance "large head."

History of Present Illness.—This child, the second, was born after a short labor, forceps being used; head presentation; birth weight was 8½ pounds. Intermittent episodes of respiratory difficulty occurred for the first three days; enlargement of the head was noted at 4 months; rapid progression of this condition continued, strabismus also being noted. No vomiting, excessive crying, or convulsions were noted. L. J. C. was unable to sit up or support her head.

Physical Examination.—The patient was a white baby girl, age 7 months; her head was obviously enlarged, the occipitofrontal circumference being 21 inches (normal 16.6 inches). There was a marked tension over the anterior fontanel. Internal strabismus was present; optic discs appeared to be normal; there was marked limitation of upward gaze; extremities moved normally. Chest circumference was 16.1 inches; x-ray examination was made which indicated hydrocephalus with thinning of the cranial bones.

The clinical diagnosis was internal hydrocephalus of communicating type.

Subsequent Course.—This baby was admitted to the hospital on April 24, 1947, and a ventricular puncture was done. The initial pressure was 330 mm. of water; 1 c.c. of indigo-carmine dye was injected and appeared promptly in the contralateral ventricle. Lumbar puncture revealed the presence of dye in the lumbar region, indicating a free communication between the ventricles and the lumbar subarachnoid. The head circumference at the time of entrance to the hospital was 21⅜ inches. A small plastic tube was introduced into the lumbar subarachnoid space and the fluid allowed to drain slowly for decompression purposes. This was followed by an abrupt rise in temperature to 102° F., which subsided after three days and was believed to be due to the decompression effect on the brain.

A right ventriculomastoidostomy was then performed, the patient tolerating the procedure well; recovery was uneventful. On May 8, 1947, the head circumference was 20¼ inches. On May 10, 1947, 2 c.c. of indigo-carmine were injected into the lateral ventricle and the dye visualized through the eardrum progressing through the middle ear indicating free drainage; this dye also appeared in the nasal dripping, when the head was held down. The baby was discharged, eating well and in excellent condition. The fontanel was soft and depressed. No medication was given.

On June 14, 1947, the patient was seen again, the mother reporting that she had had a severe bout of measles three weeks previously. She was ill for a week with elevated temperature, nasal catarrh, photophobia, and a generalized rash; her throat had been exceedingly red; she recovered uneventfully. The head circumference was 21 inches. She was able to look upward to a slight degree; there was still evidence of a bilateral sixth nerve weakness, right greater than left. She was beginning to hold her head up, ate well, and was beginning to "talk."

"On Sept. 6, 1947, head circumference 21⅛ inches; still draining fluid on pillow at night; is alert, learning readily, talking better, eating well; has been sitting up for a short time, is able to hold head up; fontanel soft.

"On Sept. 4, 1948, age 2 years. Clear liquid drainage from nose still present when she cries; learning well; able to sit up and play; began to stand several weeks before. No vomiting; speaking words well; is alert and bright. Head circumference 22 inches, chest 20¾ inches, appeared to be in better proportion to body though is still slightly larger; brow fairly prominent. Extraocular movements are normal though slightly restricted in upward gaze. No evidence of strabismus. Deep reflexes 2 plus, negative Babinski. Discs appear to be slightly pallid and flat.

"On Feb. 4, 1950 began to walk well six months previously, talking well, sings. Learns well and is very alert. Has had many severe colds with catarrh. Has had frequent sore throats but drainage persists. When she cries she drains more fluid from her nose, otherwise she drains a 3 inch spot on her pillow. There has been no marked decrease in the amount of drainage. Pneumonia two months previously, with prompt recovery. No complaints referable to the right ear. The head circumference 22⅝ inches; chest 21¼ inches.

"Optic discs are flat, and slightly pallid; fields are apparently normal; extra-ocular movements normal; hearing is intact; no nystagmus; the right ear-drum is thickened with some small vessels growing in from the lateral edges. Gait is normal, though the base appears to be slightly wider; no apparent ataxia; vibratory sense normal; deep reflexes all 2 plus; negative Babinski. Parents are highly pleased with the result and feel that she is a normal child in every respect." (Fig. 2.)

Fig. 2.—Photographs of the patient, L. J. C., three years after operation.

DISCUSSION

In the treatment of hydrocephalus where so many methods and routes of drainage have been attempted with so little success, it is not strange that the ultimate step, i.e., external drainage, should be presented again. While strictly a palliative measure, the procedure mentioned here has offered at least some prospect of success in a condition generally regarded with an attitude of hopelessness. While numerous instances of transient success with various procedures have appeared in literature, this three-year result should be regarded in the nature of a preliminary report. It may, however, be further stated that over the past year disclosure of my technique was made to other neurosurgeons* who employed it successfully in an increasing number of cases. While the possibility of a retrograde meningitis was accepted as a calculated risk, this complication has not materialized as a real threat to date. The drainage of the ventricle via a small polyethylene tubing is still continuing without obstruction over the

*Neurosurgical Division, Mayo Clinic, Rochester, Minn., Neurosurgical Division, Cleveland Clinic, Cleveland, Ohio, K. D. Abbott, M.D., Columbus Ohio, David Cleveland, M.D., Milwaukee, Wis.

three-year period. The child's development is progressing satisfactorily even though it was apparent that the cerebral cortex was considerably thinned at the time of the operation due to the enormous dilation of the ventricles. Though it is unwise to attempt any correlation between the thickness of the cortex and future intelligence, growth, development, etc., some attempt should be made to select only those patients for operation where the cerebral tissue damage is not too great, or where the head is not so disproportionately large when compared to the body, as to preclude the possibility of a reasonably normal appearance. In this patient the bodily growth has already nullified the incongruous appearance of the previously large head.

In the procedure described the drainage rate is apparently slow enough to permit some head growth, a desirable feature since one may infer that some degree of intracranial pressure exists. The existence of a negative intracranial pressure due to excessive drainage, or to the excessive loss of fluid as would occur with coughing, straining, or sneezing, seems doubtful since the diameter of the drainage tube is small and a portion of the hydraulic pressure must be dissipated in separating the opposed walls of the eustachian tube. The length of the intraventricular tube and the volume of its contained fluid, the variable intracranial pressures, when compared with the existing atmospheric pressure in the nasopharynx plus the adhesion effect of the opposed eustachian tube walls, militates against the establishment of a siphon effect in this drainage system.

It is obvious that such variations in technique as the modification of the metal tip or the substitution of a rigid metal tube for the polyethylene tubing may be made. At this time the flexible tube is preferred because it does not oppose the pulsation of the brain, hence is believed to cause less brain trauma.

It is likewise obvious that because there is no loss of spinal fluid there is no disturbance in the metabolism of the fluids, electrolytes, proteins, or carbohydrates.

CONCLUSIONS

1. The case report of a patient with marked hydrocephalus who was treated by ventriculomastoidostomy three years before is presented here.

2. Continuous ventricular drainage has been maintained for this period of time, over a hitherto undescribed pathway.

3. Brief mention is made of the advantages and disadvantages of this procedure.

REFERENCES

1. Davidoff, L. M.: Treatment of Hydrocephalus: Historical Review and Description of a New Method, Arch. Surg. **18**: 1737-1762, 1929.
2. Ingraham, F. D., Matson, D. D., Alexander, E. Jr., and Woods, R. P.: Studies in the Treatment of Experimental Hydrocephalus, J. Neuropath. & Exp. Neurol. **7**: 123-143, 1948.
3. Ingraham, F. D., Sears, R. A., Woods, R. P., and Bailey, O. T.: Further Studies on the Treatment of Experimental Hydrocephalus; Attempts to drain the Cerebrospinal Fluid into the Pleural Cavity and the Thoracic Duct, J. Neurosurg. **6**: 207-215, 1949.
4. Matson, D. D.: A New Operation for the Treatment of Communicating Hydrocephalus, J. Neurosurg. **6**: 238-247, 1949.
5. Nosik, W. A.: Ventriculomastoidostomy; Technique and Observations, J. Neurosurg. **7**: 236-239, 1950.

TRANSPOSITION OF VISCERA IN SIBLINGS

C. R. Leininger, M.D., and Stanley Gibson, M.D.
Chicago, Ill.

DURING the past few years we have encountered several cases of situs inversus viscerum, but our interest was particularly aroused recently when we observed this condition in brothers on two separate occasions. A review of the literature revealed only thirty-seven previously reported instances of transposition of the viscera in siblings. Inasmuch as situs inversus is frequently complicated by or associated with a congenital malformation of the heart, we feel that this relatively uncommon condition merits further consideration at this time.

Transposition of the viscera was first recognized by Aristotle, who described transposed organs in two animals. The first case of partial transposition of the viscera in a human being was described by Fabricius[1] in 1600, and Kuchenmeister[2] was the first individual to recognize situs inversus in a living person. With the advent of roentgenographic confirmation of transposition of the viscera by Vehsemeyer[3] in 1897, the reported incidence increased so that when Cleveland[4] reviewed the literature up to 1925 he was able to find 400 recorded cases. Johnson[5] has recently compiled 632 additional cases reported from 1925 up to 1947. He found 515 cases of dextrocardia, 379 instances of situs inversus totalis, 128 persons having an isolated dextrocardia, 41 cases of partial situs inversus, 46 involving only the colon, 20 cases involving only the great vessels of the heart, 6 cases involving only the stomach, and 2 cases where only the liver was transposed.

The incidence of transposition of the viscera in the general population as reported by different authors varies widely and depends somewhat upon the type of examination performed. Cleveland[4] reported one example in 10,000 routine dissections. In necropsy material Rösler[6] observed 3 cases in 22,402 and LeWald,[7] one case in 5,000. Sherk[8] reported 10 cases in 347,000 registrations at the Mayo Clinic over a twelve-year period, while Adams and Churchill[9] stated that 23 cases were diagnosed out of a total of 232,112 patients admitted to the Massachusetts General Hospital. During routine physical examinations of soldiers in World War I, LeWald[7] observed an incidence of one in 35,000. Gall and Woolf[10] summarized the figures from six authors and cited 74 cases occurring in 558,402 examinations. LeWald[7] has reported 29 cases in 40,000 roentgen examinations; however, he states that this does not represent a true incidence since many of the cases were referred to him because the diagnosis of situs inversus had been made. The most reliable figures are probably those obtained from autopsy material.

Familial transposition of viscera was first recorded by Rogi[11] in 1880 when he described the condition in a brother and sister. Since that time 10 additional

From the Children's Memorial Hospital, Chicago.

cases have been reported in brother and sister.[12-19, 20b] The condition has been reported in 10 sibships affecting brothers,[20a, 21-29] in 9 sibships affecting sisters,[10, 30-37] and in 7 sibships affecting 3 siblings.[29, 38-43] The condition has also been described in father and son,[44, 45] in mother and daughter,[46] in grandfather and grandson,[47] in cousins,[20a] and in uncle and nephew.[20b, 48] Araki,[49] Baumann,[50] Peters,[51] and Samoiloff[52] have also recorded cases of transposition occurring in families. The cases reported by Reinhardt, Boccia and Maglione, Cockayne, Araki, and Kean occurred in twins which were probably monozygotic. Pezzi and Carugati fail to state whether their reported twins were monozygotic or not. There are no authenticated reports of transposition of the viscera occurring in both of dizygotic twins.

Unfortunately, many of the above reports on familial transposition of the viscera are poorly documented and lack detailed descriptions. Frequently the physical examination is the only evidence demonstrating the condition and occasionally hearsay evidence is all that is available. Very few of the reports are complete with electrocardiographic proof that a true dextrocardia is present rather than dextroposition.[10, 16, 27, 32, 36, 40, 48]

In the four instances of situs inversus which we report, the electrocardiogram revealed the presence of a true dextrocardia in each instance. Two of the four patients had clinical signs of serious cardiac malformations, while another had a systolic murmur which probably represented a cardiac defect. The parents of all of these children have been examined and none has had clinical evidence of transposition of the viscera. The grandparents and great-grandparents are said to have been normal physically.

CASE 1.—J. L., a white male infant, was born on Aug. 8, 1949, and was referred to Children's Memorial Hospital at the age of 5 months. Pregnancy, labor, and delivery were uneventful. The birth weight was 10 pounds. Mild cyanosis had been present since birth. A heart murmur was first described at the age of 3 months. The child was asymptomatic except for rapid, labored breathing following episodes of crying or following vigorous nursing. The mother, age 27, and the father, age 30, were living and in good health. The only sibling is Case 2 of this report. Physical examination revealed a well-developed, well-nourished white male infant with mild cyanosis and slight clubbing of the fingers. The cardiac apex was in the fourth right intercostal space at the midclavicular line. There was a grade three, rather short, systolic murmur heard over the precordium with maximal intensity in the second right interspace near the sternum. A faint thrill was palpable in this area. The second pulmonic sound was clear and of normal intensity. Pulsations in the femoral vessels were palpable. The liver was palpable one inch below the left costal margin. Fluoroscopic examination demonstrated the heart to be suggestively boot-shaped and to lie in a reversed position in the chest with the apex and aortic arch to the right. The vascularity of the lung fields was decreased. The pulmonary window was well visualized in the right anterior oblique view and a shelf was observed in the left anterior oblique view. None of the chambers of the heart was enlarged. The liver was seen beneath the left leaf of the diaphragm. The stomach bubble was present beneath the right side of the diaphragm. Roentgenograms confirmed these findings. An electrocardiogram demonstrated a typical mirror image dextrocardia with inversion of the P and T waves and the QRS complex in Lead I. Right axis deviation was present. The red blood count was 5,510,000 per cubic millimeter

and the hemoglobin was 14 Gm. per cent. We feel that this child's condition represents a case of situs inversus with tetralogy of Fallot. Inasmuch as the baby is doing moderately well, operation is being postponed.

CASE 2.—R. L., a white male infant, a sibling of J. L., was admitted to Children's Memorial Hospital on Sept. 4, 1947, at the age of 3 weeks. His birth weight was 9 pounds, 2½ ounces, following an uncomplicated pregnancy and delivery. The neonatal period was uneventful until the third day at which time jaundice, acholic stools, and dark-colored urine were first observed. Physical examination upon admission revealed a well-developed, well-nourished infant with a generalized, mild icterus. The cardiac apex was palpable in the fourth right intercostal space at the midclavicular line. There was a short, high-pitched systolic murmur heard over the precordium but no thrill was palpable. The liver was just palpable at the left costal margin. The acholic stools, dark urine, and laboratory findings established the diagnosis of obstructive jaundice, probably due to congenital atresia of the bile ducts. A roentgenogram of the chest showed the heart to be in the right chest with the apex pointed to the right. The electrocardiogram showed typical findings of a mirror-image dextrocardia. The P and T waves and the QRS complex were inverted in Lead I. Leads II and III were transposed. The patient was discharged on Sept. 6, 1947, to return at the age of 3 months for an exploratory laparotomy. He was readmitted to the hospital on Nov. 14, 1947, for this purpose. His clinical appearance still confirmed the previous impression of obstructive jaundice. At surgery an incision was made in the left-upper quadrant and the liver was exposed. Complete dissection of the area failed to reveal bile ducts or any vestiges thereof. A tiny strand of tissue represented the gall bladder. The stomach, spleen, cecum, and appendix, as well as the liver, were all observed to be present in the left-upper quadrant. The patient had an uneventful postoperative course and was discharged ten days later. Death followed bronchopneumonia at 9 months of age. No autopsy was performed.

CASE 3.—J. A. This child was first seen at Children's Memorial Hospital on Dec. 16, 1948, at the age of 2½ years. He was born following an uneventful pregnancy, labor, and delivery. The birth weight was 9 pounds, 5 ounces. Cyanosis was observed at birth and had persisted. It was increased during episodes of crying. The parents stated that he tired easily and could walk from one-fourth to one-half block. The remainder of the history was essentially negative. The parents were living and well, the father being 38 years of age and the mother, 34. The only sibling is included in this series. Physical examination revealed a moderately well-nourished white male infant. There was a moderate generalized cyanosis and slight but definite clubbing of the fingers. The cardiac apex was palpable in the fifth right intercostal space one-half inch lateral to the midclavicular line. There was a long, harsh, grade four systolic murmur heard over the precordium with maximal intensity in the third right interspace near the sternum. The second pulmonic sound was slightly accentuated. Pulsations in the femoral vessels were palpable. The spleen was not palpated. The liver was palpable at the left costal margin.

Fluoroscopy revealed the heart in the right chest with the apex pointing to the right. The lung fields were very vascular with a hilar dance. Both ventricles were moderately enlarged. Both auricles were slightly enlarged, the right more than the left, in terms of a normally placed heart. The aortic arch lay to the right. The liver was seen on the left side and the stomach bubble was seen under the right leaf of the diaphragm. Roentgenograms confirmed the floroscopic findings. The electrocardiogram presented the typical picture

of mirror-image dextrocardia together with preponderance of the pulmonary ventricle. The red blood count was 8,320,000 per cubic millimeter. The hemoglobin was 14.25 Gm. per cent.

This patient was again seen on Sept. 13, 1949, at which time the interval history revealed that he had been getting along fairly well; however, he tired easily and could walk only two blocks without dyspnea. There was no history of squatting or paroxysmal dyspnea. Physical findings were unchanged except that the cyanosis and clubbing had increased. The fluoroscopic findings were also unchanged. The clinical impression at the present time is that this child's condition represents a case of situs inversus, probably complicated by a transposition of the great vessels with an interventricular septal defect.

CASE 4.—R. A. This child, a sibling of the infant in Case 3, was first examined on Sept. 13, 1949, at the age of 7 years. The past history was negative. Physical examination revealed a well-developed, well-nourished white male child. The cardiac apex was palpable in the fourth right intercostal space at the midclavicular line. The heart was otherwise negative. The liver was palpable at the left costal margin and there was tympany in the entire right-upper quadrant, ascribed to air in the fundus of the stomach. The physical examination was otherwise negative. Fluoroscopic examination and roentgenograms demonstrated an otherwise normal heart in the right chest with the apex pointed to the right and with a right aortic arch. The liver was demonstrable beneath the left diaphragm and the gastric bubble was apparent beneath the right leaf of the diaphragm. The electrocardiogram showed a typical mirror image dextrocardia with inversion of the P and T waves and the QRS complex in Lead I. The tracing was otherwise normal.

DISCUSSION

The etiology of visceral transposition has not been clearly established. In 1861, Foerster[53] observed the fact that in the majority of double monsters, one of them had transposed viscera. He advanced the theory, later supported by McMurrich[54] and Boeminghaus,[55] that transposition of the viscera in separate individuals represents a monozygotic twinning with the subsequent death and absorption of the twin with normally placed viscera. In 1931 Dessylla and Monticelli[56] suggested that a recessive character was the probable explanation. In a comprehensive analysis of the literature and of his own series Cockayne discounted Foerster's hypothesis and presented evidence in favor of a recessive mutation as the cause of transposition of the viscera. The present summary of the literature suggests a rather high familial incidence. One hundred nine cases, or approximately 10 per cent of those reported in the literature, have a familial relationship.

In Abbott's series[57] of 1,000 autopsied cases of congenital malformations of the heart, she reported 29 cases of dextrocardia. Eleven of these cases were situs inversus totalis. Ten cases were isolated dextrocardia with inversion of the cardiac chambers, and eight cases were isolated dextrocardia without inversion of the chambers of the heart, the term "isolated" connoting no other anomaly except that of the heart. In his series, Cockayne found 40 cases of congenital heart lesions in transposition of the viscera. The commonest anomaly was tetralogy of Fallot, being definitely present in 11 cases and possibly in 4 additional cases. In Johnson's analysis of the more recent literature, situs inversus totalis is three times more frequent than isolated dextrocardia. The

latter condition is usually associated with congenital cardiac defects. Lichtman[58] collected 161 cases from the literature, only 3 of which proved clinically and anatomically to have an otherwise normal heart. Rösler denies the existence of any uncomplicated cases in isolated dextrocardia. The general belief is that complete transposition of the viscera is only rarely associated with malformations of the heart; however, in Taussig's[59] experience, severe cardiac anomalies are also frequently found in complete transposition. Three of our four cases represent situs inversus totalis and two of these three patients had severe malformations of the heart.

SUMMARY

Transposition of the viscera has a general incidence of approximately 0.014 per cent. Over 1,000 cases have been reported in the literature. Ten per cent of these cases have occurred in families, including thirty-seven sibships in addition to twelve miscellaneous relationships.

We have added two additional sibships involving brothers in each instance. Complete situs inversus was present in 3 of the children, 2 of whom had severe congenital malformations of the heart.

REFERENCES

1. Fabricius: cited by Wood, G. O., and Blalock, A.: Arch. Surg. **40**: 885, 1940.
2. Kuchenmeister: Ibid.
3. Vehsemeyer: Ein Fall von congenitaler Detiokardie; zugleich ein Beitrag zur Verwerthung der Röntgenstrahlen in Gebiet der innern Medizin, Deutsche med. Wchnschr. **23**: 180, 1897.
4. Cleveland, M.: Situs Inversus Viscerum: Anatomic Study, Arch. Surg. **13**: 342, 1926.
5. Johnson, J.: Situs Inversus with Associated Abnormalities, Arch. Surg. **58**: 149, 1949.
6. Rösler, H.: Beiträge zur Lehre von den angeboren Herzfehlern, über die angeborene isolierte Rechtslager des Herzens, Wien. Arch. f. inn. Med. **19**: 505, 1930.
7. LeWald, L. T.: Complete Transposition of the Viscera, J. A. M. A. **84**: 261, 1925.
8. Sherk, H. H.: Total Transposition of Viscera, Surg., Gynec. & Obst. **35**: 53, 1922.
9. Adams, R., and Churchill, E. D.: Situs Inversus, Sinusitis, Bronchiectasis, J. Thoracic Surg. **7**: 206, 1937.
10. Gall, E. A., and Woolf, V. F.: Situs Inversus Viscerum Totalis in Siblings, Ann. Int. Med. **7**: 1370, 1934.
11. Rogi, E.: Storia di una transposizione dei visceri, Lo Sperimentale **14**: 376, 1880.
12. Neuhof, S.: A Case of Congenital Familial Dextrocardia, J. A. M. A. **60**: 1064, 1913.
13. Cürschmann, H.: Fämiliärer Situs Viscerum Inversus Totalis, Anatomisch. Heften **57**: 405, 1919.
14. Ochsenius, K.: Familial Situs Inversus, Monatschr. f. Kinderh. **19**: 27, 1920.
15. Brimblecombe, S. L.: Transposition of Viscera in Two Members of One Family, Brit. M. J. **2**: 889, 1920.
16. Cahan, J. M.: Transposition of All the Viscera, M. J. & Record **122**: 75, 1925.
17. Hofmann, A. H.: Familial Situs Inversus, Zentralb. F. Chir. **53**: 1633, 1926.
18. Bianchi, S.: Case Report, Riv. Med. **35**: 189, 1927.
19. Manson, J. S.: Two Cases of Transposition of the Viscera in One Family, Brit. M. J. **1**: 1171, 1935.
20. Cockayne, E. A.: The Genetics of Transposition of the Viscera, Quart. J. Med. **7**: 479, 1938.
    a. 1 case
    b. 2 cases
21. Reid, D. McK.: Transposition of the Viscera Occurring in Brothers, Lancet **1**: 717, 1909.
22. Lowenthal, L.: Transposition of the Viscera Occurring in Brothers, Lancet **1**: 461, 1909.
23. Leroux, C., Labbé, R., and Barret, G.: Inversion viscérale totale, Bull. Soc. pédiat. de Paris **14**: 297, 1912.
24. Reinhardt: Ein Fall von Situs viscerum inversus totalis bei zwillingen (Rekruren), Deutsche. mil-ärztl. Ztschr. **41**: 931, 1912.
25. Pezzi, C., and Carugati, L.: Cuore E circolazione, Roma **8**: 361, 1924.

26. Boccia, D., and Maglione, R.: Dos Casos de "Situs Viscerum Inversus," Rev. sud-am. de endocrinol. **10:** 705, 1927.
27. Körner: Situs inversus totalis bei zwei Brudern, Röntgenpraxis **9:** 197, 1937.
28. Carpenter, G.: Congenital Morbus Cordis: Complete Transposition: Transposition of Liver, Spleen and Large Intestine: Cyst in Tongue: Solitary Kidney, Proc. Roy. Soc. Med. (Study Dis. Child) **223:** 1908, 1909.
29. Torgersen, J.: Familial Transposition of Viscera, Acta med. Scandinav. 126: 319, 1946.
30. Günther, H.: Die biologische Bedeutung der Inversionen, Biol. Zentralbl. **43:** 175, 1923.
31. Maekawa, T.: Aichi-Igakkai-Zasshi **34:** 481, 1927 (cited by Cockayne).
32. Müller-Pollak, F.: Über das Electrokardiogramm bei Kindern mit Situs inversus, Monatschr. f. Kinderh. **43:** 475, 1929.
33. Mittelbach, F.: Med. Klin. **26:** 784, 1930 (cited by Cockayne).
34. Nätvig, H.: Familiaer situs inversus totalis, Nord. med. **1:** 681, 1939.
35. Feldman, M., and Needle, N.: Complete Transpositions of the Viscera in Siblings, Radiology **34:** 97, 1940.
36. Kean, B.: Complete Transposition of the Viscera in Both of One-egg Twins, J. Hered. **33:** 217, 1942.
37. LeWald, L.: cited by Kean.
38. Carpenter, G.: cited by Cockayne.
39. Frölich, T.: Forh. med. Selsk. i Kristiania, 1920 (cited by Feldman and Needle).
40. Liotta, D.: Situs viscerum inversus complicato a stenosi dell' arteria polmonare e communicazione interventricolare, Riforma med. **43:** 869, 1927.
41. Oshima, M.: Grenzgebiet **11:** 1509, 1929 (cited by Cockayne).
42. Matsueda, A.: Okayama-Igakkai- Zasshi **41:** 1929 (cited by Cockayne).
43. Feldman, W.: Transposition of Viscera, Behaving as a Mendelian Recessive Character with Congenital Absence of the Appendix, Proc. Roy. Soc. Med., London **28:** 753, 1935.
44. Doolittle, W.: Congenital Dexiocardia, Boston M. & S. J. **157:** 662, 1907.
45. Meyer-Hürlimann: Med. Klin. **12:** 525, 1916 (cited by Cockayne).
46. Matisson, K.: Ztschr. f. Konstitutionslehre, Berlin **17:** 325, 1933 (cited by Cockayne).
47. Randolph, B. M.: Case of Transposition of Viscera Showing Heredity, New York M. J. **82:** 1053, 1905.
48. Boruttau and Stadelman: Leitfaden der klinischen Electrokardiographie, page 21, 1917 (cited by Rösler).
49. Araki, B.: Nagasaki-Igakkai-Zasshi **12:** 640, 1935 (cited by Cockayne).
50. Baumann: Acht Fälle von Situs inversus viscerum totalis, Inaug. Diss., Zurich, 1917 (cited by Rösler).
51. Peters: Cited by Cockayne.
52. Samoiloff: Cited by Cockayne.
53. Foerster, A.: Die Missbildung des Menschen, Jena, 1861, p. 136.
54. McMurrich, J.: The Development of the Human Body, ed. 7, P. Blakiston's Son & Company, Philadelphia, 1923, p. 49.
55. Boeminghaus, H.: Ueber Dickdarmanomalie bei Situs Inversus, Deutsche Ztschr. f. Chir. **155:** 174, 1920.
56. Dessylla, C., and Monticelli, M.: Cardiopatie congenite in casi di destrocardia congenita con e senza eterotassi, Riv. di radiol. e. fis. med. **3:** 657, 1931.
57. Abbott, M.: Atlas of Congenital Cardiac Disease, New York, 1936, American Heart Association.
58. Lichtman, S.: Isolated Congenital Dextrocardia, Arch. Int. Med. **48:** 683-717, 866-903, 1931.
59. Taussig, H.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund.

COMBINED IMMUNIZATION OF TUBERCULOUS CHILDREN AGAINST DIPHTHERIA, PERTUSSIS, AND TETANUS

MANFRED WEICHSEL, M.D., AND ABRAM HODES, M.D.
LONG ISLAND CITY, N. Y.

ACTIVE immunization of susceptible children against diphtheria, smallpox, pertussis, and tetanus is a well-established procedure in pediatric practice. The combined prophylaxis against two of the three diseases, diphtheria and tetanus, has been in use for several years. The combined immunization against diphtheria, tetanus, and pertussis as a routine prophylaxis for well children has obvious advantages.[1] It has been shown that such combinations have a synergistic effect[2-5] and reduce the number of injections.

Following injections of potent vaccine normal children will produce demonstrable antibodies within a few days to weeks. This basic immunity persists for long periods of time. A second stimulus months to years later will afford protection almost immediately. If mixtures of toxoids or toxoids and vaccines are employed, the immunity thus acquired seems to be superior to that acquired by injection of one alone, inasmuch as the immunity produced is enhanced.[6, 7]

The routine immunization of children against tetanus which is an accepted pediatric procedure has raised some interesting questions which are of great practical importance. The actual level of tetanus antitoxin necessary to confer clinical immunity is not definitely known. If the conventional dose of 1,500 units of tetanus antitoxin is injected in the prophylactic treatment of a wound, titers of 0.2 to 0.5 unit of antitoxin per cubic centimeter of serum will be obtained very rapidly. This level falls to 0.1 unit per cubic centimeter of serum during the second week and to 0.01 unit during the third week. Ratner[6] believes that although 0.01 unit per cubic centimeter of serum may be adequate for minor tetanus infections, 0.1 unit is preferable.

A condition known as "basic immunity" is demonstrable after active immunization and seems to persist for several years. The blood antitoxin level may be extremely low but increases rapidly following a "booster" dose. The patient possesses the ability to respond quickly with a protective amount of antitoxin. Miller and Ryan,[8] however, believe that the enhanced capacity to respond rapidly with antitoxin formation to a secondary stimulus may not be all that is necessary in active immunization against tetanus. They cite experimental evidence to prove that the inoculation of animals with tetanus spores may fail to act as secondary stimulus and insist on biennial stimulating injections of tetanus toxoid in an effort to maintain at all times a level of tetanus antitoxin which may be protective in itself. Miller and his co-workers[9] have recently cited war cases where tetanus occurred despite immunization following extensive trauma or heavy contamination.

From the Pediatric Service of Sea View Hospital, Staten Island, N. Y.

This type of disease is characterized by short incubation periods, sometimes even less than one week, and a high fatality rate. The reinjection of toxoid on wounding in two such cases failed to prevent death. The authors suggest that maximal protection in severely wounded individuals, or when immunization occurred more than four years previously, should be obtained by simultaneous injection of antitoxin and toxoid in different extremities. In minor wounds or scratches on the other hand, a reinjection of toxoid alone is sufficient.

In the case of tuberculous children, especially those confined to a hospital or sanatorium, the need for prophylactic immunization against contagious diseases seems to be obvious. Attacks of pertussis in particular should be avoided since this disease may seriously impair the child's general condition, weaken the resistance, and lead to deterioration of the tuberculous process. The resistance of the host is influenced by the presence of secondary infections, among other factors. The belief, however, that pertussis predisposes to miliary tuberculosis and tuberculous meningitis has been challenged by various investigators. Siegel and Goldberger[10] found that whooping cough had no specific effect on tuberculosis in twenty-five children studied. They believe, however, that a focus in the lungs in open communication with the air passages may spread by the bronchogenic route under the effect of the convulsive attacks of coughing which spread the infective exudate and secretions to higher levels along the bronchial tree. The infectious material may then be carried to healthy parts of the lungs by the deep inspirations which follow the attack of coughing. They consider this danger of whooping cough more important than other factors, as for example the lowering of the tuberculin sensitivity. Toomey and his co-workers[11] have recently pointed out that in no case of tuberculosis save one could any evidence be found on which to base the conclusion that the tuberculosis was activated by pertussis.

What are the contraindications against the performance of such prophylactic measures as active immunization of tuberculous children against pertussis, diphtheria, and tetanus? Our knowledge about the effect of these inoculations on the tuberculous process is limited. There appears to be a conception among many pediatricians that routine inoculations of the type performed may be detrimental to the health of the tuberculous child and lead to aggravation or flare-up of tuberculous lesions. Siegel and Goldberger[12] found no evidence to support the view that tuberculosis per se diminishes the effectiveness of whooping cough vaccines. In previous work we[13, 14] could show that tuberculous children responded to whooping cough vaccine much like normal children. The complement fixation test was strongly positive one week after completion of vaccination and remained positive in tests done one month after the last dose of vaccine. Furthermore, in inoculations against diphtheria there was no difficulty in immunizing tuberculous children with toxoid as determined by the conversion of a Schick positive reactor to a Schick negative reactor.

For the past few years we have attempted to protect all tuberculous children in the pediatric wards by active immunization against diphtheria, pertussis, and tetanus. Active immunization against scarlet fever and influenza is also highly desirable but outside the scope of this article.

MATERIALS AND METHODS

For the purpose of this study two groups of children were immunized. The first group of children received a "combined antigen."* It contained per cubic centimeter 20 Lf (limit of flocculation) of diphtheria toxoid, 12 Lf of tetanus toxoid, and a detoxified pertussis filtrate which had been concentrated by ultrafiltration. The second group of children was immunized with Tri-Immunol.* The fluid Tri-Immunol contained 20 Lf of purogenated diphtheria toxoid, 12 Lf of purogenated tetanus toxoid, and 30 billion phase I pertussis organisms per dose (1.0 c.c.); whereas the other type of Tri-Immunol was made to include the same amounts of toxoids and 10 billion alum-precipitated pertussis organisms per dose (0.5 c.c.). An immunizing course consisted of 3 injections at three- to four-week intervals. A fourth dose was occasionally given where the primary immunization appeared to be inadequate. The inclusion of purogenated toxoid in this material is based on the work of Pillemer.[15] The toxoids are 99.7 per cent nitrogen-free, the nonantigenic nitrogen having been reduced to 0.15 per cent approximately. In the alum-precipitated forms, the alum content has been decreased by 75 per cent, thus reducing to a minimum any local reaction caused by that substance. The antigenic property of these new toxoids is so highly concentrated that the dosage required is only one-half the volume usually required with standard toxoids. Ruegsegger and Looser[16] inoculated 31 adults and 550 children with these alcohol-refined toxoids of diphtheria and tetanus. They believe that such toxoids stimulate an adequate and durable immunity as judged by serial antitoxin titrations.

All injections were given subcutaneously in the deltoid area. These were a number of children in each group where repeated bleedings over a period of several months were obtained. The children in both groups ranged in age from 10 months to 8 years. Although more than 50 children were given prophylactic injections in the first group, only 34 could be used for statistical purposes due to losses by discharge, transfer, etc. Initial inoculations were given at weekly intervals to 11 children and at three- to four-week intervals to 23 children. The period of observation ranged from several weeks to two and one-half years. The amount of Combined Antigen injected in each case was 3 c.c. Booster doses were given to 29 subjects in this series. Of the 34 children immunized, 26 were suffering from primary pulmonary tuberculosis, 6 had chronic reinfection type of tuberculosis, and in 2 cases tuberculosis was doubtful. The symptoms were severe in 5, moderate in 17, and mild in 12 children.

There were 35 children immunized with three injections of Tri-Immunol. Some of these received the fluid type of this material; the majority was given the alum-precipitated form. Injections were done at three- to four-week intervals.

RESULTS

Only evaluation of the serum levels of diphtheria and tetanus antitoxin will be attempted in this report. Results of determination of antipertussis antibodies have been reported previously.[13, 14, 17] We were able to show that

*Kindly supplied by Lederle Laboratories.

pertussis antigen as contained in the Combined Antigen was capable of raising the titers of complement-fixing antibodies in many cases. It also raised the titers of pertussis antitoxin in a fair percentage of children. Results of titrations of antipertussis antibodies in the serum of children treated with Tri-Immunol which contains bacterial vaccine will be reported later.

From Table I it appears that adequate levels of diphtheria antitoxin were obtained in all children. Six months after the third injection of Combined Antigen two children showed titers of 0.1 to 0.5 unit per cubic centimeter of serum, one child of 0.5 to 1.0 unit, and two children of more than 1.0 unit. Of 27 titrations done one year or more after completion of the injections, 11 showed titers of 1.0 unit or more and all of them at least 0.1 to 0.5 unit. This level of circulating antitoxin is compatible with a negative Schick test and indicates definite immunity. These figures are of interest if we consider that 11 of the 34 children in this series received their injections at one-week intervals and 23 at three- to four-week intervals. However, some of these patients may have had a residual immunity to diphtheria based on previous active immunization unknown to us which could have potentiated the efficacy of the present series of injections. The results of the booster doses were likewise adequate. The stimulating dose consisted of either 0.2 c.c. of fluid diphtheria toxoid or 0.2 c.c. of Combined Antigen. Every one of the children tested in this series exhibited high titers of circulating diphtheria antitoxin when tested four weeks after the stimulating dose.

TABLE I. DIPHTHERIA ANTITOXIN TITRATIONS FOLLOWING THREE INJECTIONS OF "COMBINED ANTIGEN"

66 ANTITOXIN TITERS (UNITS)	TIME ELAPSED AFTER THIRD INJECTION								
	4 WK.	2 MO.	4 MO.	6 MO.	9 MO.	1 YR.	1½ YR.	2 YR.	2½ YR.
0.01 to 0.1				1	1				
0.1 to 0.5	1	1	2	2		5	3		
0.5 to 1.0	4			1		5	1		2
more than 1.0	3	2	1	2		4	5	1	1
After injection of booster doses of either diphtheria toxoid or "Combined Antigen"									
0.1 to 0.5									1
0.5 to 1.0							2	4*	
more than 1.0					1	6	14	5	4†

*One test was done 18 months after the booster dose.
†Two tests were done 18 months after the booster dose.

The levels of tetanus antitoxin in the serum of children injected with three doses of Combined Antigen were definitely inferior to the titrations of diphtheria antitoxin. Four weeks after the third injection ten sera showed less than 0.1 unit per cubic centimeter, five of them less than 0.01 unit. Of twelve sera tested six months after completion of this series five showed less than 0.01 unit per cubic centimeters. The response was much better if we consider the titers observed after a booster dose of either 0.2 c.c. of fluid tetanus toxoid or 0.5 c.c. of Combined Antigen. Bleedings were obtained regularly after four weeks unless mentioned in the table. Thus, thirteen children tested after one year showed titers of 0.1 unit or more and eleven children tested after two years likewise were above this level.

TABLE II. TETANUS ANTITOXIN TITRATIONS FOLLOWING THREE INJECTIONS OF "COMBINED ANTIGEN"

ANTITOXIN TITERS (UNITS)	TIMES ELAPSED AFTER THIRD INJECTION									
	4 WK.	2 MO.	4 MO.	6 MO.	9 MO.	1 YR.	1½ YR.	2 YR.	2½ YR.	3 YR.
less than 0.01	5	4		5		3	2	2		
0.01 to 0.1	5	2	3	6		4				
0.1 to 1.0	9	1	2	1	2	2	1			
more than 1.0	2		1		1					
After injection of booster doses of either "Combined Antigen" or tetanus toxoid										
less than 0.01						2*	1†	1*		
0.01 to 0.1					1	1†	6	1†	1*	
0.1 to 1.0				2	2	4	7	3	4	1‡
more than 1.0				2	1	9		8	2	1

*Done six months after the booster dose of "Combined Antigen."
†Done eight months after the booster dose of 0.2 c.c. of tetanus toxoid fluid.
‡Done two years after the last booster dose.

TABLE III. DIPHTHERIA ANTITOXIN TITRATIONS FOLLOWING THREE INJECTIONS OF TRI-IMMUNOL

ANTITOXIN TITERS (UNITS)	2 WK.	1 MO.	2 MO.	4 MO.	6 MO.	9 MO.
0.01 to 0.1		1				
0.1 to 0.5		1				
0.5 to 1.0		1		1	1	1
more than 1.0	1	13	2	6	10	2
Total Tests	1	16	2	7	11	3

Of sixteen children tested one month following the third injection of Tri-Immunol, fifteen sera showed high titers of diphtheria antitoxin. All children tested after six and nine months exhibited good titers. All injections of Tri-Immunol were administered at four-week intervals.

TABLE IV. TETANUS ANTITOXIN TITRATIONS FOLLOWING THREE INJECTIONS OF TRI-IMMUNOL

ANTITOXIN TITERS (UNITS*)	TIME ELAPSED AFTER THIRD INJECTION					
	2 WK.	1 MO.	2 MO.	4 MO.	6 MO.	9 MO.
0.01 to 0.1						
0.1 to 1.0				1	1	2
more than 1.0	1	18	2	9	6	2
Total Tests	1	18	2	10	7	4

*Units refer to American units per ml. of serum.

The results of the titrations of tetanus antitoxin were very satisfactory. Of eighteen sera tested one month after completion of the injections none showed a level of less than one unit. After six and nine months respectively all children gave adequate response their titers being 0.1 unit or more.

A careful follow-up of these children by clinical examination, laboratory work, and x-ray failed to show any evidence of a detrimental effect of these prophylactic injections on their tuberculous process. True, many of our patients obviously had latent tuberculosis of no great extent. Some were afebrile and showed very few signs of active tuberculosis. Others, however, had smaller or larger shadows at the hilum of the lung, tracheobronchial lymph node

tuberculosis, fever, constitutional symptoms, and an elevated sedimentation rate; others had reinfection type of tuberculosis. The course of the tuberculosis in these cases was entirely unaffected by these inoculations. The advantages to be derived from these measures outweigh the possible ill effects. No plausible reason can be given for withholding necessary prophylaxis.

The results of numerous titrations of serum for diphtheria and tetanus antitoxin showed a difference of titers depending on whether the Combined Antigen or Tri-Immunol was used. In the former the percentage of children showing an adequate response to basic immunization against tetanus was decidedly less than in the Tri-Immunol group. The difference was less marked when a comparison is made between the two groups based on the results of the diphtheria antitoxin titrations. This may be due to the fact that some of these children have had some form of basic immunity against diphtheria before they were started on injections of Combined Antigen.

In the case of tetanus immunization we believe the high titers following Tri-Immunol injections were due to (1) better antigenicity of the purogenated toxoid; (2) the presence of alum which retards absorption, and (3) the longer spacing of the injections.

COMMENT

It is apparent from our observations that the immunization procedure applied in the tuberculous child is not harmful, for in no instance could we determine any exacerbation of the tuberculous process. We believe that the benefits derived far outweigh any possible fear that some previous authors have raised.

The antitoxin levels resulting from the vaccinations were in all instances equal to those obtained in the nontuberculous child.

Because of the serious consequences that might result from cases of pertussis, particularly in the young infant with primary tuberculosis and because serious consequences might ensue from serum sickness resulting from injection of diphtheria antitoxin, we believe that all sanatoriums caring for tuberculous children should institute a comprehensive program for active immunization and booster doses in the childhood population in order to give these children the same advantage that is afforded nontuberculous children. This is particularly true for children who are eventually discharged and mingle with an immunized population.

SUMMARY AND CONCLUSIONS

1. Sixty-nine tuberculous children treated on the pediatric wards of Sea View Hospital were immunized with two forms of combined antigens. ("Combined Antigen" and Tri-Immunol.)

2. The best results were obtained by injections of Tri-Immunol. High titers of tetanus and diphtheria antitoxin were observed which persisted for several months.

3. The results of serum titrations for tetanus antitoxin were somewhat disappointing when three injections of "Combined Antigen" administered at

weekly intervals were given. The titers were higher when the basic immunization was performed by three injections administered at three-week intervals. Results of injections of "booster doses" were satisfactory.

4. Results of titrations of diphtheria antitoxin were good in all cases. The possibility of previous unknown prophylactic immunization is discussed.

5. No detrimental effects on the course of tuberculosis was observed.

6. It is recommended that active immunizations against diphtheria, tetanus, and pertussis with periodic booster doses become the rule with children confined to sanatoriums.

I am indebted to Dr. B. Ratner, Chief of Service, for his suggestions in the preparation of this manuscript.

REFERENCES

1. Lapin, J. H.: Combined Immunization of Infants Against Diphtheria, Tetanus, and Diphtheria, Am. J. Dis. Child. **63**: 225, 1942.
2. Bigler, J. A., and Werner, M.: Active Immunization Against Tetanus and Diphtheria in Infants and Children, J. A. M. A. **116**: 2355, 1941.
3. Lapin, J. A.: Mixed Immunization in Infancy and Childhood, J. PEDIAT. **22**: 439, 1943.
4. Miller, J. J., Jr., Humber, J. B., and Dowrie, J. O.: Immunization With Combined Diphtheria and Tetanus Toxoids (Alum Hydroxide Absorbed) Containing *H. pertussis* Vaccine, J. PEDIAT. **24**: 281, 1944.
5. Miller, J. J., Jr.: Immunization Procedures in Pediatrics, J. A. M. A. **134**: 1064, 1947.
6. Ratner, B.: Allergy, Anaphylaxis, and Immunotherapy, Baltimore, 1943, Williams & Wilkins Company.
7. Ramon, G.: Mixed Vaccinations, Internat. Clin. **1**: 241, 1939.
8. Miller, J. J., Jr., and Ryan, M. L.: Immunization With Combined Diphtheria and Tetanus Toxoids (Aluminum Hydroxide Absorbed) Containing *H. pertussis* Vaccine II. Duration of Serologic Immunity, Pediatrics **1**: 1, 1948.
9. Miller, J. J., Jr., Ryan, M. L., and Beard, R. R.: The Speed of the Secondary Immune Response to Tetanus Toxoid With a Review of the War Reports and Observations on the Simultaneous Injection of Toxoid and Antitoxin, Pediatrics **3**: 64, 1949.
10. Siegel, M., and Goldberger, E. W.: Am. J. Dis. Child. **57**: 506, 1939.
11. Toomey, J. A., Berno, J. C., and Agustsson, H.: J. PEDIAT. **32**: 260, 1948.
12. Siegel, M., and Goldberger, E. W.: J. A. M. A. **109**: 1088, 1937.
13. Weichsel, M., Katona, N., and Liu, Flora: Am. J. Dis. Child. **64**: 1, 1942.
14. Weichsel, M., and Douglas, H. S.: J. Clin. Investigation **16**: 15, 1937.
15. Pillemer, L., Wittler, R., and Grossberg, D. B.: Science; **103**: 615, 1946. Pillemer, L., and Toll, D.: Science: **105**: 102, 1947.
16. Ruegsegger, J. M., and Looser, G. K.: Pediatrics **2**: 35, 1948.
17. Weichsel, M., Rubin, H. J., Cohen, P., and Lapin, J. H.: Am. J. Dis. Child. **60**: 862, 1940.

THE SKELETAL LESIONS OF LEUCEMIC CHILDREN TREATED WITH AMINOPTERIN*

FELIX E. KARPINSKI, JR., M.D., AND JAMES F. MARTIN, M.D.
CLEVELAND, OHIO

THE occurrence of skeletal lesions in children suffering from acute leucemia is well known and the literature contains numerous reports of roentgenographically demonstrable changes. Since von Jaksch,[1, 2] in 1901, first described the roentgen changes in the long bones of a patient with leucemia, numerous isolated case reports have appeared. One of the first reviews of skeletal changes in leucemia was that of Snelling and Brown,[3] and Erb[4] in 1934. They described five types of pathologic changes: (1) infiltration, (2) rarefaction, (3) proliferation, (4) degeneration, and (5) hemorrhage. Baty and Vogt,[5] in 1935, further emphasized leucemic bone changes and described transverse bands of diminished density across the growing ends of long bones in 70 per cent of 43 children with leucemia who were studied radiographically. Kalayjian, Herbut, and Erf,[6] in 1946, reviewed the available literature and found reports of 144 leucemic children who showed demonstrable bone changes in roentgenograms and added 2 more cases. Silverman,[7] in 1948, reported on 103 children with acute leucemia, 52 of whom showed skeletal changes in their roentgenograms. In his series osteolysis was noted in 39 patients, radiolucent transverse bands in 14, periosteal new bone formation in 17, and osteosclerosis in 9. Dale,[8] in 1949, briefly described the literature and emphasized three types of lesions in 72 per cent of 40 children with acute leucemia. He did not report osteosclerotic lesions and described these as late changes resulting from stimulation of osteoblasts and new bone formation or fibrous and osseous repair of destroyed areas within bone.

With the introduction of the folic acid antagonists in the treatment of acute leucemias, numerous workers reported varying degrees of success with this form of therapy. Emphasis was placed on the hematologic and clinical responses obtained; however, little attention was given to the effect of these antagonists on the skeletal lesions. It remained for Silverman,[9] in 1949, to report his observations in a small series of seven leucemic children treated with Aminopterin, whose long bones were studied roentgenographically. Skeletal lesions were said to regress in all cases, and of greater significance was the failure of these children to develop new lesions. He described the appearance of heavy, transverse bands of increased density at the ends of the shafts of long bones following the administration of Aminopterin. According to Silverman these bands develop as a result of alteration of endochondral bone formation by the drug.

In a recent study one of us[10] reported our experiences in 24 children with acute leucemia treated with the folic acid antagonists. One of these patients

From the Department of Pediatrics and the Department of Radiology of Western Reserve University School of Medicine, and of Babies and Childrens Hospital, Cleveland, Ohio.

*Aminopterin was generously supplied by the Lederle Laboratories Division, American Cyanamid Company, through the courtesy of Dr. Benjamin W. Carey.

(Case 6) developed a destructive lesion in the distal third of the left radius which regressed remarkably during treatment with Aminopterin. As a result of this observation a roentgen survey was undertaken to see what effect, if any, Aminopterin had on the skeletal lesions of children with acute leucemia.

In all, 35 children with acute leucemia were included in the study. The patients were admitted to the hospital for diagnosis and initial treatment. The diagnosis of leucemia was based upon characteristic changes in the bone marrow in all cases. Upon discharge from the hospital all patients were followed in the Leucemia Clinic. Visits to the clinic were made three times weekly. All but one patient (Case 1) of this group received Aminopterin therapy.

The roentgen survey of these children with acute leucemia included studies of the chest, skull, long bones, and occasionally the lumbodorsal spine and pelvis. Roentgenograms were obtained in thirty-three children and the incidence of lesions in this series is recorded in Table I.

TABLE I

PART EXAMINED	NO. OF PATIENTS EXAMINED	NO INITIAL LESION	INITIAL LESION PRESENT	NO INITIAL LESION BUT APPEARED LATER	TOTAL LESION
Chest	33	26	7	5	12
Skull	27	23	4	2	6
Long Bones	33	11	22	5	27

Chest.—The chest roentgenogram revealed evidence of abnormality in twelve of the cases during the course of the disease. Five patients developed lesions within the chest even though the initial survey study was normal. The lesions identified included enlargement of the hilar nodes, pleural effusion, parenchymal infiltration and hemorrhage, passive hyperemia, and pulmonary edema. The serial film studies fail to demonstrate any evidence of regression of the lesions during the course of Aminopterin therapy.

Skull.—Lesions of the skull were infrequent and were identified in six cases. Osteolysis was the only type of lesion identified and is thought to be due to destructive foci of leucemic cells which arise in the diploic space and erode the neighboring compact bone of the tables of the skull.[11] This was more prominent in the later stages of the disease and the progress of the lesions appeared to be uninterrupted by Aminopterin therapy. Many of the patients developed a granular appearance to the skull which may represent an early manifestation of hyperplasia of the bone marrow.

Widening of the suture lines of the skull was an unexpected finding which occurred in four patients. This is usually interpreted to represent an increase in intracranial pressure and probably represents either intracranial hemorrhage or leucemic infiltration within the brain and meninges.

Long Bones.—The long bones revealed evidence of abnormality at the initial examination in 66 per cent of the cases, which is the highest incidence in this series. Five patients developed lesions during the period of observation so that 81 per cent had roentgenographic evidence of bone involvement during the course of the disease. It seems probable that this percentage might be even

higher if all cases had intensive serial roentgen studies. The most common site of change was in the ends of the shafts of the long bones. The roentgenograms of the knees and ankles demonstrate the lesions well. Occasionally, the osteolytic lesions are first identified in the lumbodorsal spine or pelvis.

Osteolysis was identified in twelve cases, subperiosteal new bone formation in eleven, and transverse bands of diminished density at the ends of the shafts of the long bones were present in twenty-two. True osteoclerosis was not identified in this series. Two or more types of lesions were frequently encountered simultaneously.

The transverse bands of diminished density at the ends of the shafts of the long bones were the most common lesions identified and appeared to represent the most frequent early roentgen finding in the bones of children with acute leucemia. We are not certain as to the nature of this change, but the observation in one of our patients (Case 1) leads us to believe that these bands of translucence represent a disturbance of metabolic function produced by the disease rather than an actual invasion of the ends of the long bones by leucemic cells. This change is also present in other diseases such as scurvy, syphilis, and other chronic diseases associated with malnutrition. Osteolytic lesions may develop at these sites and these are believed to represent an actual infiltration of leucemic cells which may be a later manifestation of the disease. The subperiosteal new-bone formation is believed to be due to an infiltration of the periosteum by leucemic cells with subsequent stimulation to produce these changes.

Thirteen of the patients had adequate serial film studies to permit evaluation of the roentgen changes that occurred during this period. Five of these patients had no evidence of a lesion in the long bones at the initial examination, but four of these developed changes during the course of Aminopterin therapy. Eight of the patients had evidence of a lesion in the long bones at the initial examination. Of these, two remained unchanged, one regressed, and five demonstrated progression of the lesions despite Aminopterin therapy.

An additional finding was the presence of transverse bands of increased density at the ends of the shafts of the long bones. This feature was identified in five cases in this series. In one patient (Case 4), this band was demonstrated on the initial roentgenogram before therapy with Aminopterin was instituted. Another child (Case 1), who had never received Aminopterin, developed these bands during a spontaneous remission. The remaining three patients developed these lesions during the course of treatment with Aminopterin. The nature of this change is not clearly understood, but perhaps they may represent evidence of improvement in the general nutrition of the bone. It is altogether possible that they represent the heavy, transverse bands of increased density reported by Silverman[9] who ascribes this change to an alteration of endochondral bone formation by Aminopterin. These bands appeared to represent a transient change and became less prominent as the disease progressed.

CASE 1.—K. P., a 4-year-old white female child, was admitted to Babies and Childrens Hospital of Cleveland on Aug. 16, 1949, with a four-week's history of fever, listlessness, pallor, intermittent pain in the lower extremities, weakness,

and anorexia. Admission examination revealed marked, generalized pallor of the skin and mucous membranes, generalized shotty, nontender lymphadenopathy, and hepatosplenomegaly. There were no petechiae or ecchymoses.

Laboratory studies showed: erythrocytes 1,220,000 per cubic millimeter, hemoglobin 3.0 Gm. per 100 ml., leucocytes 1,400 per cubic millimeter, with 100 per cent lymphocytes on the differential smear. The sternal marrow contained 99 per cent blast cells. The initial roentgen examination of the chest on Aug. 17, 1949, revealed slight elevation of the left side of the diaphragm. There was no evidence of lesions in the skull but slight generalized osteoporosis was present in the long bones.

Aminopterin therapy was suggested but the child's parents preferred not to have this treatment instituted and the patient was discharged on the fourth hospital day.

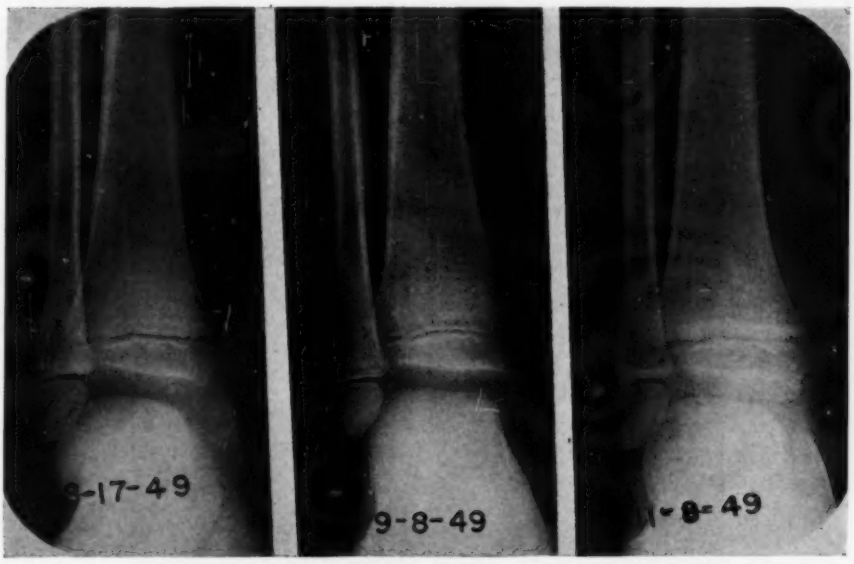


Fig. 1.—Slight osteoporosis of right ankle present on Aug. 17, 1949. Appearance of a transverse band of decreased density by Sept. 8, 1949. Development of a heavy band of increased density on Nov. 8, 1949, following a spontaneous remission.

She was readmitted on Sept. 7, 1949, with a two-week's history of tonsillitis, fever, and purulent discharge from the left eye and ear. Examination was essentially the same as on the previous admission with the exception of the following: the lids of the left eye were edematous, red, crusted, and covered with a thick, purulent discharge. Both auditory canals were filled with a serosanguineous discharge and the tympanic membranes appeared perforated. Treatment consisted of penicillin, streptomycin, and aureomycin along with several small transfusions. Sternal aspiration at this time revealed an extremely hypoplastic marrow with only 0.5 per cent blast cells.

The roentgen studies of Sept. 8, 1949, revealed a slight increase in the elevation of the left side of the diaphragm; there was a definite transverse band of diminished density at the ends of the shafts of the long bones, and a slight increase in the generalized osteoporosis. No lesion was identified in the skull.

The patient was discharged on the fifteenth hospital day with little clinical or symptomatic relief. Since Sept. 24, 1949, this patient has been seen twice weekly in the Leucemia Clinic. She has remained in complete remission, both hematologic and symptomatic, without any specific therapy. Serial roentgenograms have been obtained with the following results.

On Nov. 8, 1949, there was no change in the roentgen appearance of the skull and chest, but a dense, horizontal band of increased density had developed at the ends of the shafts of the long bones. The osteoporosis of the long bones was less marked at this time.

Evidence suggesting slight osteolysis in the frontal and parital bones of the skull was present on the examination of Jan. 3, 1950. No change was identified in the chest roentgenogram. The long bones had become slightly osteoporotic and the dense, transverse bands of density in the long bones had become less prominent.

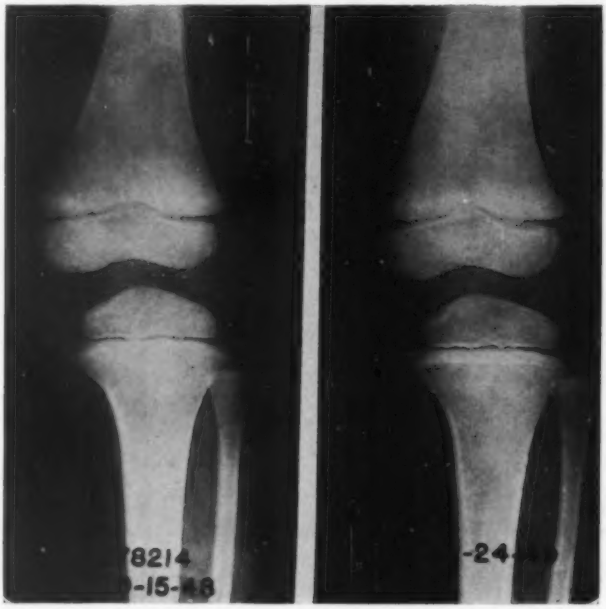


Fig. 2.—Appearance of a transverse band of increased density during Aminopterin therapy. The initial roentgenogram on Oct. 15, 1948, was normal.

CASE 2.—J. B., a 4-year-old white male child, was admitted to Babies and Childrens Hospital of Cleveland on Oct. 14, 1948, with a history of pallor, listlessness, and easy bruising for a period of two weeks. Physical examination revealed moderate pallor, numerous petechiae and ecchymoses, generalized lymphadenopathy, and hepatomegaly.

Laboratory studies were as follows: erythrocytes 2,300,000 per cubic millimeter, hemoglobin 8.6 Gm. per 100 ml., leucocytes 4,300 per cubic millimeter, with a differential of segmented neutrophiles 12 per cent, unsegmented neutrophiles 2 per cent, lymphocytes 40 per cent, and blast cells 36 per cent. The sternal marrow contained 86.8 per cent blast cells.

The roentgen examination of the chest, skull, and long bones on Oct. 15, 1948, revealed no abnormalities at that time.

The child was treated with Aminopterin 1.0 mg. daily for fourteen days. He responded well to therapy. Another examination of the marrow on Oct. 29, 1949, revealed 11.0 per cent blast cells. He was discharged much improved on the thirty-first hospital day.

During the next four months the child attended the Leucemia Clinic and treatment with Aminopterin was continued. He appeared healthy, happy, and was free of symptoms. However, on Feb. 24, 1949, he developed pain in the right knee and refused to walk. Otherwise his appetite was excellent, he felt well and the physical examination was essentially negative.

A roentgen examination on Feb. 24, 1949, revealed transverse bands of increased density at the ends of the shafts of the long bones. There was no evidence of osteolysis or subperiosteal newbone formation.

For some unknown reason this patient never returned to the clinic and further studies could not be done. However, we learned that he expired in May, 1949, seven months after the onset of the disease.

CASE 3.—R. S., a 19-month-old white male infant, was admitted to Babies and Childrens Hospital of Cleveland on Oct. 30, 1948, with a three-week's history of anorexia, pallor, and easy bruising. Physical examination at the time of admission revealed pallor, numerous petechiae and ecchymoses, generalized lympadenopathy, and marked hepatosplenomegaly.

Laboratory studies were as follows: erythrocytes 2,700,000 per cubic millimeter, hemoglobin 8.0 Gm. per 100 ml., leucocytes 35,000 per cubic millimeter, with a differential of segmented neutrophiles 5 per cent, unsegmented neutrophiles 5 per cent, lymphocytes 38 per cent, and blast cells 52 per cent. The sternal marrow was found to contain 92.6 per cent blast cells.

The initial roentgen studies on Nov. 6, 1948, revealed a slight osteoporosis at the ends of the shafts of the long bones. There was no evidence of lesions in the chest or skull.

The patient received Aminopterin in 0.5 mg. doses daily for period of eleven days. Several small blood transfusions were also given. There was definite hematologic and symptomatic improvement and he was discharged on the twenty-seventh hospital day.

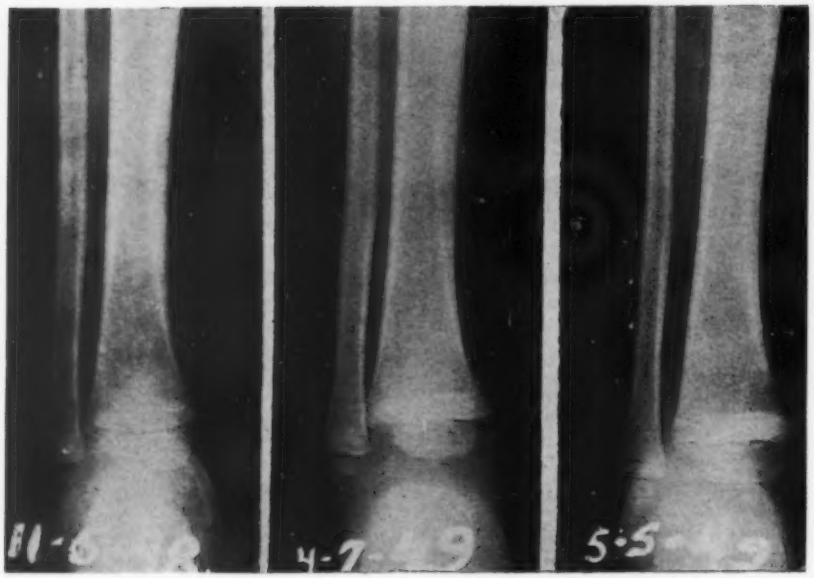
For the next four months the child was seen three times weekly in the Out Patient Clinic. Therapy with Aminopterin was continued and he appeared healthy and happy. In May of 1949, the patient suffered a relapse and was readmitted to the hospital.

The roentgen examination on May 5, 1949, revealed osteolytic lesions and subperiosteal new bone formation in the long bones. An unusual line of subcortical osteoporosis had developed in the bones of the foot and ankle. The sutures of the skull were widened and the bones were osteoporotic. The transverse diameter of the heart had increased abnormally and the vascular markings in the lungs were quite prominent.

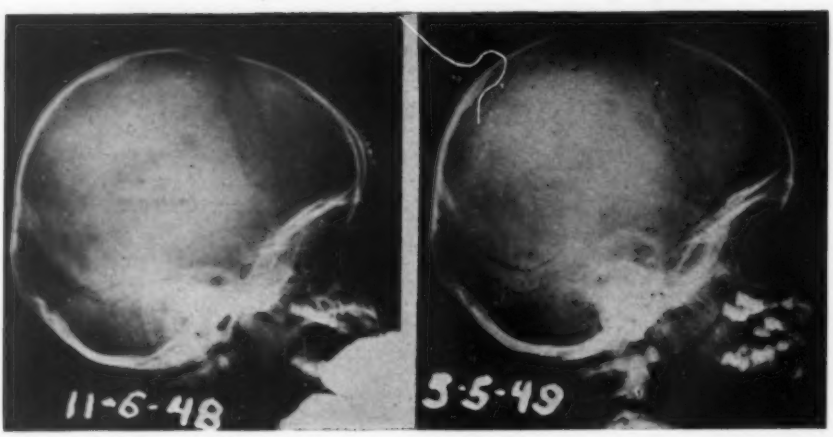
The vascular markings of the lungs had become increased on May 15, 1949, and a transverse band of radiolucence had developed at the ends of the shafts of the long bones.

A roentgenogram of the chest on May 18, 1949, revealed an extensive homogenous density in the medial portion of the right lung and mottled areas of increased density in the left lung and the peripheral portion of the right lung.

Despite numerous blood transfusions this patient's condition became progressively worse and he expired on May 20, 1949.



A.



B.

Fig. 3.—*A*, Illustrates slight improvement in the bony architecture during treatment with Aminopterin. Osteolysis and subperiosteal new bone formation are present, however, on May 5, 1949.

B, Slight widening of the suture lines of the skull in the terminal phase of the disease.

CASE 4.—M. M., a 3-year-old white female child, was admitted to Babies and Childrens Hospital of Cleveland on June 25, 1948. For three weeks she had experienced progressive fever, malaise, and anorexia. Leg pain was noted on one occasion. A progressive pallor had also been noted. Admission physical examination revealed marked pallor, slight hepatosplenomegaly, generalized nontender lymphadenopathy, and absence of petechiae or ecchymoses.

Laboratory studies revealed: erythrocytes 1,920,000 per cubic millimeter, hemoglobin 5.0 Gm. per 100 ml., leucocytes 3,300 per cubic millimeter, with a differential of granulocytes 3 per cent, lymphocytes 95 per cent, monocytes 1 per cent. The sternal marrow contained 98.8 per cent blast cells.

The initial roentgen study of the chest and skull on June 29, 1948, revealed no abnormality. There was a band of increased density at the ends of the shafts of the long bones and a slight generalized osteoporosis.

Fig. 4.—Heavy transverse band of increased density on initial roentgenogram before treatment with Aminopterin. The film on the right shows increase in the osteoporosis with little change in the heavy band despite therapy with the drug.

She received Aminopterin daily for a period of nine days, and several small blood transfusions. Improvement was gradual with recession of the liver, spleen, and lymph nodes until they were no longer palpable. The sternal marrow was re-examined on the twentieth hospital day and was found to contain only 4.0 per cent abnormal cells. She was discharged on the twenty-first hospital day.

For five weeks following discharge the patient was asymptomatic. Four months after her initial admission to the hospital, she again developed fever, anorexia, and pain in the right foot and left arm. Examination at this time revealed generalized pallor, moderate generalized lymphadenopathy, hepatosplenomegaly, and several ecchymoses. Examination of the extremities and joints was not remarkable.

Laboratory studies at this time were: erythrocytes 3,500,000 per cubic millimeter, hemoglobin 8.0 Gm. per 100 ml., and leucocytes 4,000 per cubic millimeter.

The roentgen examination on Oct. 12, 1948, revealed an increase in the osteoporosis in the long bones and subperiosteal new bone formation. The transverse bands of increased density at the ends of the long bones were present and had not changed significantly. The chest and skull appeared normal.

She received a course of intensive Aminopterin therapy, improved markedly, and was again discharged after a fourteen-day stay in the hospital. In the ensuing months her course was progressively downhill and she expired Jan. 24, 1949. A bone marrow sample shortly before death revealed marked hypoplasia.

Fig. 5.—Progression of osteoporosis and osteolysis in the long bones of a patient treated with Aminopterin.

CASE 5.—L. V. T., a 4-year-old white female child, was admitted to Babies and Childrens Hospital of Cleveland on Feb. 13, 1949, with a three-week's history of pallor, listlessness, and fever. There was no bone pain or bleeding tendency. Initial examination revealed marked, generalized pallor of skin and mucous membranes, shotty discrete, generalized lymphadenopathy, and hepatomegaly.

Laboratory studies were as follows: erythrocytes 860,000 per cubic millimeter, hemoglobin 1.5 Gm. per 100 ml., leucocytes 14,900, with a differential of neutrophiles 12 per cent, and lymphocytes 88 per cent. A sample of sternal marrow contained 100 per cent blast cells.

The initial roentgen examination on Feb. 14, 1949, revealed slight, generalized osteoporesis in the long bones but no evidence of disease in the skull or chest.

Treatment consisted of Aminopterin 1.0 mg. daily for thirteen days and several small blood transfusions. The patient responded well to therapy and was discharged on the fourteenth hospital day.

For the next six months she was seen at regular intervals in the Leucemia Clinic. Her condition was never satisfactory and she required numerous admissions to the hospital for blood transfusions and intensive Aminopterin therapy. Repeated examinations of the marrow failed to reveal a significant reduction in the number of blast cells.

A roentgen survey on June 8, 1949, four months after the initial examination revealed small osteolytic lesions at the ends of the long bones. The transverse diameter of the heart had increased slightly and there was a slight increase in the vascular markings of the lungs.

Osteolysis in the long bones had become a more prominent feature by July 2, 1949, and faint areas of cortical erosion were easily identified.

Subperiosteal new bone formation, increasing osteoporosis, and osteolysis were present on Aug. 11, 1949. There was slight pleural thickening about both lungs but no change in the size and contour of the cardiac silhouette.

The child was admitted to the hospital for the last time in August, 1949. She failed to respond to repeated blood transfusions and expired on Aug. 29, 1949, seven months after the onset of the disease.

CASE 6.—R. S., a 3½-year-old white male child, was admitted to Babies and Childrens Hospital of Cleveland on May 27, 1948. He had been well until December, 1947, when he developed bouts of fever, anorexia, and migratory joint pains. Admission physical examination revealed moderate pallor, generalized lymphadenopathy, and hepatomegaly. The left elbow and wrist were swollen, hot, and tender to touch. There also was moderate swelling and tenderness of the proximal phalanx of the middle finger of the left hand.

Laboratory studies revealed: erythrocytes 2,600,000 per cubic millimeter, hemoglobin 9.5 Gm. per 100 ml., leucocytes 21,000 per cubic millimeter, with a differential of neutrophiles 5.0 per cent, lymphocytes, 37 per cent, monocytes 3.0 per cent, and blast cells 54 per cent. The sternal marrow contained 96.8 per cent blasts.

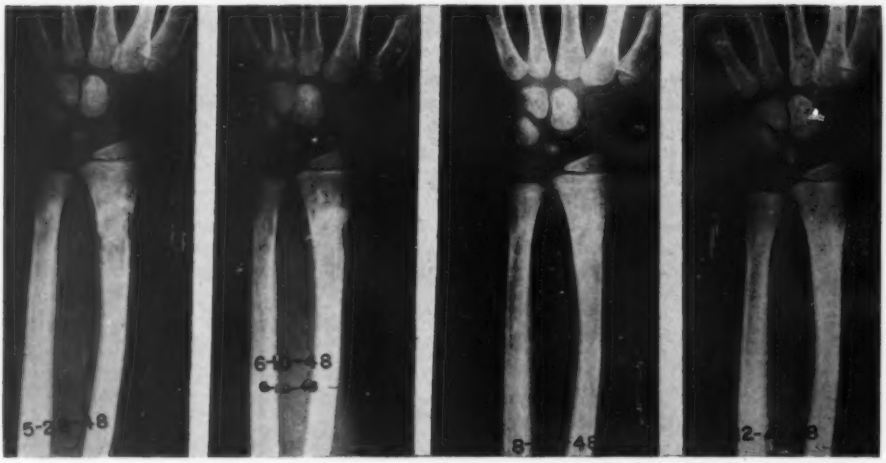
The initial roentgen study of the chest and skull on May 28, 1948, revealed no evidence of disease. There was generalized osteoporosis of the lumbodorsal spine, pelvis, and long bones. A line of subperiosteal new bone formation was present along the right ulna. There was a destructive lesion 2 cm. in length in the shaft of the distal left radius with adjacent subperiosteal new bone formation.

Treatment consisted of Aminopterin 1.0 mg. daily. After five days of therapy the swelling, pain, and tenderness of the left-upper extremity disappeared.

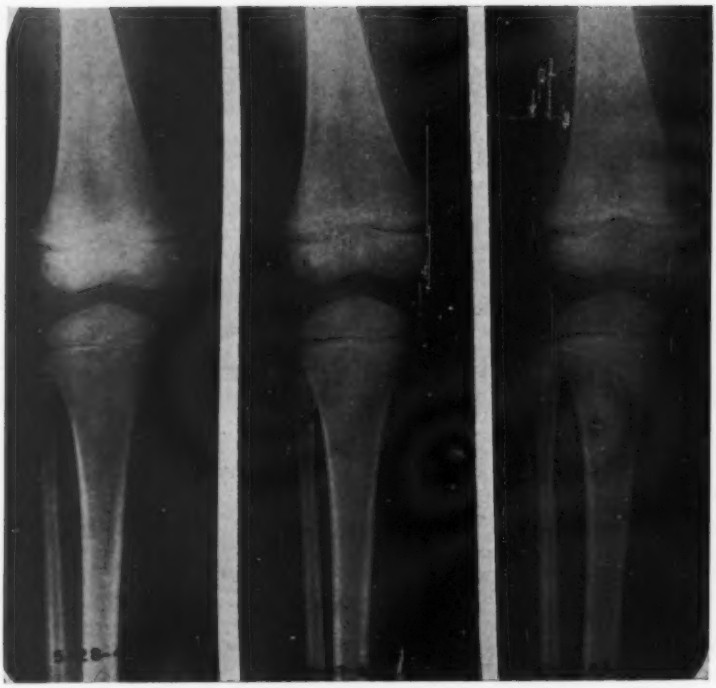
Roentgen examination on June 10, 1948, after eight days of Aminopterin therapy, revealed marked healing of the destructive lesion in the distal end of the left radius, but no significant change in the generalized osteoporosis or the subperiosteal new bone formation.

For the next week the patient continued to show symptomatic and hematologic improvement. Examination of the marrow at this time revealed only 19.6 per cent blast cells. Roentgenograms on June 17, 1948, demonstrated further healing of the lesion of the distal end of the left radius with a decrease in the adjacent subperiosteal new bone formation.

The patient's improvement was dramatic and he was discharged on the twenty-third hospital day.



A.



B.

Fig. 6.—*A*, Generalized osteoporosis and a destructive lesion 2 cm. in length in the distal shaft are identified in the initial films of May 28, 1948. Subsequent studies show rapid and complete healing of the lesion following therapy with Aminopterin. *B*, Films of the knee illustrate the response to Aminopterin with a decrease in the osteoporosis and an increase in the density at the ends of the shafts of the long bones.

For the next ten weeks the patient was asymptomatic and his appearance and activities appeared normal in all respects. A roentgen study of the long bones on Aug. 27, 1948, revealed little evidence of the destructive lesion of the left radius, and the osseous architecture had a normal appearance. Slight, generalized osteoporosis was noted in the long bones and there was a marked decrease in the subperiosteal new bone formation. There had been a slight increase in the density at the ends of the long bones.

For the next eight months his course was one of alternating periods of remission necessitating countless transfusions and repeated admissions to the hospital. Repeated examinations of bone marrow samples revealed an active marrow with almost total replacement by blast cells.

Roentgen examination of the long bones on Dec. 4, 1948, revealed no significant change.

The child's last hospital admission was on April 25, 1949. Death came forty-eight weeks after therapy with Aminopterin was instituted.

CASE 7.—E. J., a 7-year-old white boy, was admitted to Babies and Childrens Hospital of Cleveland on April 7, 1949, with a six-month's story of intermittent fever, severe migratory joint and bone pains, anorexia, pallor, and weakness. Admission physical examination revealed moderate pallor of the skin and mucous membranes and splenomegaly.

Laboratory studies were as follows: erythrocytes 2,860,000 per cubic millimeter, hemoglobin 8.5 Gm. per 100 ml., leucocytes 16,500 per cubic millimeter. with a differential count of segmented neutrophiles 42 per cent, unsegmented neutrophiles 11 per cent, lymphocytes 39 per cent, monocytes 3 per cent, and basophiles 3 per cent. The sternal marrow revealed 88.6 blast cells.

The roentgen study on April 11, 1949, revealed marked osteoporosis of the ribs, skull, dorsal spine, and pelvis. There were early osteolytic lesions in the skull and pelvis. There were compression fractures of dorsal vertebrae 7, 8, and 11. The long bones revealed marked generalized osteoporosis, early cortical osteolysis, and a transverse band of diminished density at the ends of long bones which measured approximately 6 ml. in width.

The patient was treated with Aminopterin 1.0 mg. daily for thirteen days. At the end of this period he appeared much happier, was free of pain, and his appetite had improved immeasurably. He was discharged on the sixteenth hospital day.

For the next six and one-half months he attended the clinic at regular intervals and Aminopterin therapy was continued. His peripheral blood studies remained within normal limits. However, during all this time the patient was unable to walk and occasionally complained of pain over the spine.

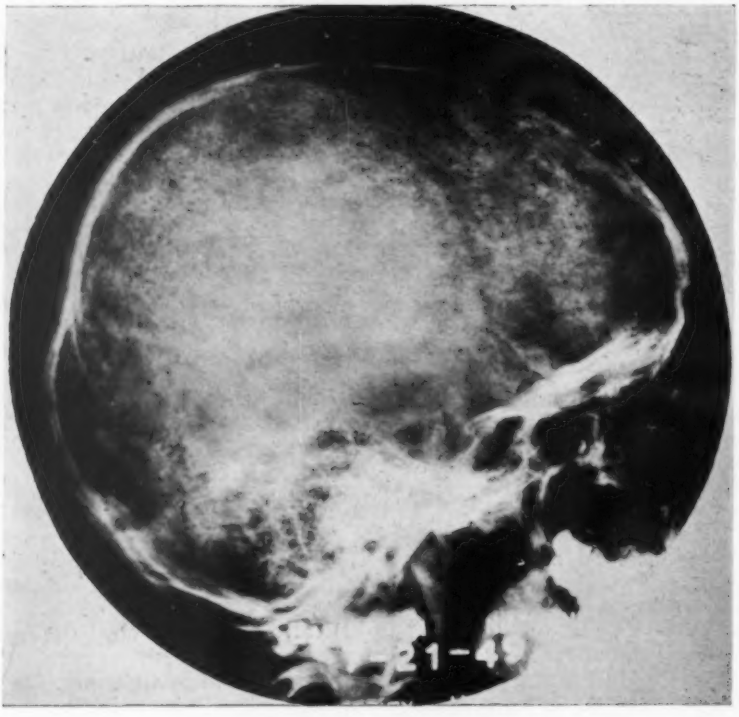
The roentgen examination on May 19, 1949, demonstrated an increase in the osteolysis of the skull. There was increasing osteoporosis evident in the long bones. Compression fractures were noted in the lower 6 dorsal and upper 3 lumbar vertebrae.

Roentgen studies on July 21, 1949, revealed an increase in osteolysis and osteoporosis and subperiosteal new bone formation was noted along the shafts of most of the long bones. The changes were more marked in the lower extremities. There was a marked increase in the extent of the osteolytic lesions in the skull.

On one occasion he bumped his right knee and developed considerable swelling of the joint. Roentgen films on July 28, 1949, revealed an increase in the osteolysis and osteoporosis of the right knee with an impacted fracture of the distal end of the right femur.

The remainder of the patient's clinical course was unsatisfactory. Roentgen studies on Aug. 30, 1949, revealed extensive cortical destruction of the long

A.



B.

Fig. 7.—*A*, Films of the knee show marked osteoporosis, early osteolysis, and a wide band of diminished density on April 11, 1949. Progression of lesions despite Aminopterin is illustrated by July 28, 1949. *B*, Extensive osteolysis of the skull in the same patient.

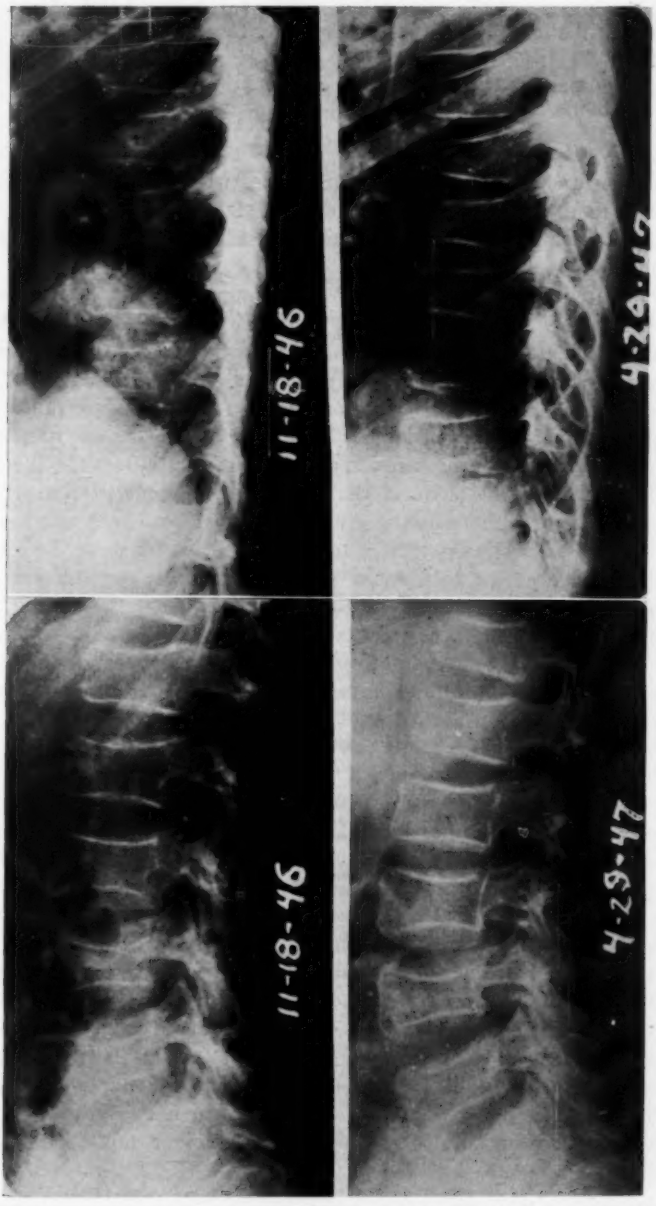


Fig. 8.—Note temporary improvement in the osseous architecture of the vertebral bodies following therapy with radioactive phosphorus (P^{32}). Case history not included.

bones and epiphysis of the right ankle. The transverse band of radiolucence at the ends of the long bones was more marked than at the initial examination.

On Sept. 27, 1949, this patient was seriously injured in a minor automobile accident, sustained multiple fractures of the hips and lower extremities, and expired two hours later.

COMMENT

It has been accepted that Aminopterin can produce temporary clinical and hematologic remissions in the acute leucemias of childhood, but it is impossible to state with certainty that the drug has a specific effect on the various skeletal lesions observed in the disease.

Although evidence is presented of the disappearance of a true destructive bone lesion in one patient R. S. (Fig. 6) during treatment with Aminopterin, one cannot attribute these dramatic changes to the drug per se. It is possible that such bony defects are reversible during a remission of the disease, whether it be spontaneous or induced by various agents. The disappearance of transverse bands of diminished density has been observed during spontaneous remissions when there was improvement in the patient's nutrition.[8, 9] We have also observed marked improvement in the osteoporotic lesions of the vertebrae in one patient treated with radioactive phosphorus. (Fig. 8.) From the observations in this series of cases, it would appear that progression of the bone lesions occurred despite therapy with Aminopterin and there was no correlation with the clinical or hematologic response to the drug.

The development of heavy transverse bands of increased density at the ends of the long bones of patients treated with Aminopterin needs explanation. There was nothing to indicate exposure to any of the heavy metals which could produce similar bands. The roentgenograms of one patient, K. P. (Fig. 1), illustrate that these heavy bands can develop during a spontaneous remission in the disease. In another patient, M. M. (Fig. 4), heavy transverse bands were present on the initial roentgen examination before Aminopterin therapy was instituted. Therefore, the pathogenesis of these transverse bands remains obscure and it cannot be stated categorically that they arise as a result of a specific effect of Aminopterin on endochondral bone formation. It is possible that these changes represent an improvement in the nutrition of the bone during a remission, whether it be spontaneous or induced by Aminopterin.

Furthermore, there is no conclusive evidence to indicate that Aminopterin will prevent the formation of new bone lesions as evidenced by four patients who developed demonstrable skeletal changes during treatment with the drug.

It is by no means clear why the response of the skeletal lesions to Aminopterin should be so variable. It may be related to the stage of the disease in which the patient is first observed or to some factor not as yet recognized. Indeed, further investigation is indicated for a clearer understanding of this problem.

1. Roentgen observations were made of the skeletal lesions in a group of thirty-five children with acute leucemia.

2. Lesions of the chest, skull, and long bones are described.

3. Dramatic disappearance of a true destructive lesion was observed in one patient treated with Aminopterin.

4. The identification of heavy transverse bands of increased density at the ends of the long bones of treated and untreated children with leucemia is discussed.

5. Aminopterin apparently does not prevent the development of new bone lesions.

6. The specific action of Aminopterin on the skeletal lesions in acute leucemias cannot be stated with certainty.

REFERENCES

1. von Jaksch, R.: Multiple Periostaffection und an myelogene Leukämie mahnender Blutbefund, Prag. med. Wchnschr. 26: 19, 1901.
2. von Jaksch, R.: Multiple Periostaffection und an myelogene Leukämie mahnender Blutbefund, Ztschr. f. Heilk., Abt. f. inn Med. 22: 259, 1901.
3. Snelling, C. E., and Brown, A.: Bone Changes in Leukaemia, Arch. Dis. Childhood 9: 315, 1934.
4. Erb, I. H.: Bone Changes in Leukaemia; Pathology, Arch. Dis. childhood 9: 319, 1934.
5. Baty, J. M., and Vogt, E. C.: Bone Changes of Leukemia in Children, Am. J. Roentgenol. 34: 310, 1935.
6. Kalayjian, B. S., Herbut, P. A., and Erf, L. A.: The Bone Changes of Leukemia in Children, Radiology 47: 223, 1946.
7. Silverman, F. N.: The Skeletal Lesions in Leukemia, Am. J. Roentgenol. 59: 819, 1948.
8. Dale, J. H., Jr.: Leucemia in Childhood: A Clinical and Roentgenographic Study of Seventy-two Cases, J. PEDIAT. 34: 421, 1949.
9. Silverman, F. N.: Roentgenographic Changes in the Long Bones of Leukemic Children Treated with Aminopterin. Read before Society for Pediatric Research, May, 1949.
10. Weber, E. J., Karpinski, F. E., and Heinle, R. W.: The Treatment of Acute Leucemias of Childhood with Folic Acid Antagonists, J. PEDIAT. 36: 69, 1950.
11. Caffey, J.: Pediatric X-Ray Diagnosis, Chicago, 1945, The Year Book Publishers, Inc., p. 70.

FUNNEL CHEST: ITS CAUSE, EFFECTS, AND TREATMENT

CHARLES W. LESTER, M.D.
NEW YORK, N. Y.

FUNNEL CHEST is generally considered to be rather uncommon in spite of the fact that an accurate description of it appeared in the literature in 1600[1] and articles about it have been appearing ever since. This may be because most physicians consider it of slight importance and that nothing can be done about it anyway. If the profession becomes aware of the physical and psychologic consequences of the deformity and realizes that the deformity can be corrected, more cases will undoubtedly appear. To that end, the deductions from the study of forty-two cases in which operation was done and an additional number without operation are presented.

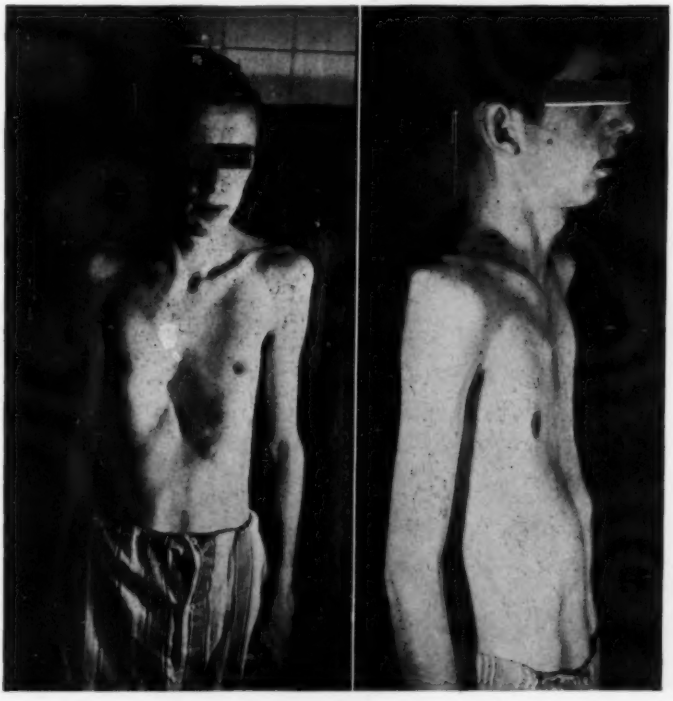
Funnel chest (pectus excavatum, trichterbrust, thorax en entonnoir, etc.)* is a funnel-shaped deformity of the anterior chest wall involving the sternum and costal cartilages. The apex usually corresponds to the xiphoid but may be to the right or left of it. The periphery of the funnel commences at the angle of Louis, or just below it, and the depression also involves the abdominal wall within the costal arch. (Fig. 1.) During inspiration the depression deepens.

The defect is congenital and shows marked hereditary tendencies. Two brothers in this series are the sons of a man who also had a deep funnel chest and who died of pulmonary tuberculosis; and a large number of the other patients have parents or relatives with funnel chest. The sexes are about equally represented.

The mechanism producing the deformity was obscure until Brown[3] noticed that the depression was deeper during inspiration and correctly concluded that it was caused by a short central tendon of the diaphragm which retracted the lower end of the sternum and the substernal ligament during inspiration. He also called attention to the fact that the author of the article published in 1600 had made the same observation. The diaphragm is normally domed when relaxed, as in expiration. When contracted, as in inspiration, it tends to flatten out, thereby increasing the longitudinal dimensions of the chest cavity and hence its volume. If the central tendon is short the maximum flattening is soon attained and further contraction serves only to approximate the diaphragmatic attachments, or, when the shortening is in the middle of the central tendon, to draw the xiphoid backward toward the vertebral column. This produces the funnel-shaped depression. Thus the amount of depression over the xiphoid and the amount of its retraction are directly proportionate to the amount of shortening of the central tendon. If the shortening is in the center the funnel will be in the midline and will also be symmetrical.

*In the matter of nomenclature *funnel chest* seems to me to be the most practicable term. It is descriptive and is the English translation of the other names except *pectus excavatum*. As Ochsner and DeBakey[2] point out, the condition is neither *pectus* nor *excavatum*, so the Latin terminology has nothing to recommend it except an aura of erudition for the user. Ochsner and DeBakey coined a descriptive name from the Greek, *chone chondrosternon*, but this seems rather cumbersome.

However, the deformity is not always central and not always symmetrical. If the central tendon is short laterally as well as centrally there will be, in addition, a transverse groove across the chest similar to the Harrison's groove of rickets. If the shortening is proportionately greater in the lateral leaflets of the tendon than in the central portion, the funnel may be slight or even absent and the transverse groove may be the dominant feature. (Fig. 2.) If the maximum shortening of the tendon is to the right or left of the center, the maximum depression of the chest wall will correspond to it and, hence, the deformity will be asymmetrical. For some unknown reason these asymmetrical deformities have the depression more often on the right than on the left.



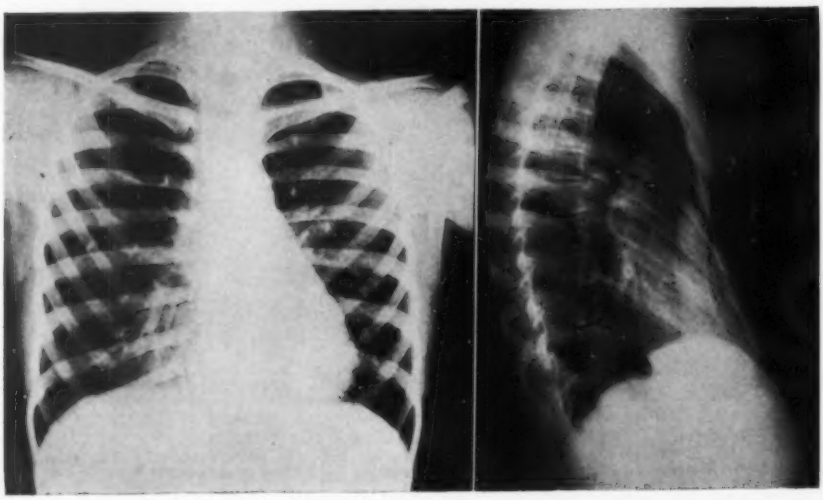
A. *B.*

Fig. 1.—*A*, Funnel chest in boy, aged 19 years. Note the narrow chest, round shoulders, and poor development. Prior to operation the patient could not remember when he was free from cough.

B, After the operation; the depression is about 80 per cent corrected, but narrow chest remains. Cough is now absent most of the time and exercise tolerance has increased 300 per cent.

The statement is made[4] that chronic upper-respiratory obstruction, such as would occur with large adenoids or tonsils, may be a cause of funnel chest. My own opinion is that such obstruction has little or no effect on the production of the deformity. In the first place, most of the patients suffering from funnel

Fig. 2.—Transverse groove without funnel in a child aged 5 years. Pulmonary resection on left (for pulmonary tuberculosis) subsequently permitted observation of the traction exerted by the short lateral leaflet of the central tendon.



A. *B.*

Fig. 3.—*A*, Posteroanterior roentgenogram of the chest of an 8-year-old girl with funnel chest. Note downward slant of the anterior ends of ribs.

B, Lateral view of same patient showing depressed sternum, round back, and narrow chest. The depression is of moderate severity, but the heart was not able to escape to the left and the patient had low exercise tolerance and heart murmur. Operation corrected the depression 85 per cent, removed the heart murmur, and permitted normal development. Five years later she still has a slight sternal depression and a narrow chest but has passed through the change of puberty and appears entirely normal.

chest do not have such obstruction; and in the second place, when the obstruction is present the lower end of the sternum retracts just as much during inspiration when an endotracheal tube is in place and the airway is free. Nevertheless, if such an obstruction is present, correction of it is advised before undertaking any surgical procedure on the deformity.

The extent of the deformity next depends upon the amount of change produced in the ribs, which are pulled down and back by the sternal depression. In an infant the ribs are pliable and resilient. They yield readily to compression and traction and when the force is relaxed they tend to spring out to their normal position. As the child gets older the resiliency lessens and the deformity of the ribs and sternum becomes fixed. After the child is about one year old, the backward curve of the sternum seems to be established. The ribs, however, do not seem to become fixed in an abnormal position until the child is 4 or 5 years old. The effect of the retraction of the xiphoid is, thus, to curve the sternum backward and in so doing draw the ribs down and back which, in turn, decreases the anteroposterior dimensions of the chest. (Fig. 3.) The backward pull on the sternum also acts to increase the normal dorsal curvature of the spinal column thus producing a round back and, hence, stooped shoulders. Furthermore, the sternal depression, the narrow chest, and the exaggerated dorsal curvature of the spine make the abdomen appear unduly prominent and protruberant. Hence an individual with funnel chest appears round-shouldered, hollow-chested, and potbellied. (Fig. 4.)

Other congenital deformities are not uncommon. These may have little bearing on the chest condition but should be mentioned. In the patients of this series there have been fused ribs, abnormal vertebrae, clubbed feet, cryptorchidism, polycystic kidney, defective dentition, faulty breast development, and retarded mentality.

Changes in the thoracic cage will, obviously, have their effect on the thoracic organs. As regards the lungs, pulmonary volumes are decreased about 25 per cent in advanced cases, which, of itself, is not a significant figure and does not explain the frequent symptoms of cough and susceptibility to respiratory infections that these patients often exhibit. These symptoms may be due to a kinking of the bronchi due to the deformity but are probably best explained on the basis of an ineffectual cough because of restricted respiratory excursions. Secretions which would ordinarily be expelled by a good cough remain to prolong a respiratory infection that, in a normal person, would be of minor importance.

The heart is responsible for more symptoms than are the lungs and the severity of the cardiac symptoms is directly proportional to the pressure exerted on the heart by the retracted sternum. In most instances the heart is displaced to the left as the sternum encroaches on the mediastinum (Fig. 3), and if the heart can move out of the way a deep funnel may produce only moderate symptoms. On the other hand, if the heart cannot escape to the left a moderate funnel may produce incapacitating symptoms. In severe cases the patients are bedridden and in nearly all patients with a definite funnel there is some decrease in exercise tolerance. In judging this symptom it must be remembered that

the patient is not aware of a moderate restriction because he has never experienced his normal capacity for exercise. He usually does realize it after the pressure has been relieved by operation because he finds that he can do so much more. The symptoms of underweight and retarded physical development are also usually present, as they are in any chronic cardiac condition.

A. *B.*

Fig. 4.—*A*, Funnel chest in child aged 3 years. Note the round shoulders and potbelly. The chest is not yet appreciably narrowed.

B, Same patient immediately after operation. The depression is corrected and subsequent growth eliminated the potbelly and poor posture.

On auscultation a systolic murmur is frequently heard. This is so noticeable that many of these patients are considered to have rheumatic hearts and are treated for this condition rather than for the funnel chest. The murmur disappears after the sternum has been elevated. Electrocardiographic changes are also relatively common but they do not follow any definite pattern. The most common finding is a right axis deviation which is explained by assuming that the sternal depression rotates the heart to the right as well as displaces it to the left. Elevation of the sternum does not immediately change the electrocardiogram.

So far only the physical and physiologic effects of the deformity have been discussed but the psychologic effects are no less important and frequently over-

shadow the others. The patients recognize their deformity at any early age and it is not uncommon to see children of 4 or 5 years of age acutely aware of their difference from their playmates. As they grow older they shun the beaches, gymnasiums, and athletic fields; and after the age of puberty the girls are keenly conscious of their hollow chests which even the most effective "falsies" are unable to correct.

The surgical correction of physical deformities for cosmetic reasons is decried by many physicians, but in this connection it is repeated that physical restrictions are not always recognized by the victims and it is logical to assume that when the physical defect is of sufficient magnitude to produce psychologic reactions, there are also physical restrictions.

The treatment of funnel chest is, of course, surgical and the type and extent of the operation depends upon the age of the patient. In infants one year old or less a simple type of operation can be expected to produce a good percentage of favorable results. Beyond that age skeletal changes have developed which require a radical operation for their correction. As the radical operation necessitates an endotracheal anesthesia, we prefer to wait until the child is 2½ years old before operating, but would rather not wait beyond the age of 5 years. After that age permanent changes in ribs and thoracic cage begin to appear and, while the pressure symptoms can be relieved the deformity may not be completely corrected. The oldest patient in this series to undergo operation was 40 years old and the increased exercise tolerance he obtained made the operation well worth while although the deformity was only about 75 per cent corrected.

The simple and radical operations described by Brown,[3] in 1939, were the first to produce uniformly good results because they were the first to take cognizance of the underlying pathologic condition. With increasing experience the procedures have been modified by Brown himself[7] and by others, including the author,[5, 6] but the basic principle of removing the pull on the lower end of the sternum and then elevating the sternum to a normal position remains. The operations we employ have been described in detail elsewhere.[6]

The simple operation used in infants consists in making an incision over the lower end of the sternum and exposing the xiphoid by resecting as much of the costal arch as is necessary. The xiphoid is then detached from the sternum by incising the xiphisternal junction and entering the mediastinum by dividing the substernal ligament. The wound is then closed and reliance is put on the resiliency of the chest wall and the growth of the child to correct the deformity.

This simple procedure is inadequate to correct the deformity once it has been established and a more radical operation is employed. This is performed through a longitudinal, midline incision extending from the second sternal segment to the level of the bottom of the costal arch. Subperichondrial resection of the third to the seventh or eighth costal cartilages is next done on both sides, followed by a transverse wedge osteotomy across the third sternal segment through the outer table only, leaving the posterior table intact. The xiphoid is then detached from the sternum by incision through the xiphisternal

junction, dividing the underlying substernal ligament and entering the ventral mediastinum. The sternum is then elevated to a normal position by producing an incomplete fracture along the line of the wedge osteotomy and held in this position by two wires passed across the back of the sternum through two pairs of drill holes and carried out through the muscles and skin onto the chest wall on either side of the incision. The ends of the wires are twisted into a ladder-like support placed transversely across the chest after closing the wound. In two weeks the costal cartilages have regenerated sufficiently to afford stability to the chest wall making it possible to remove the ladder and wires without danger of paradoxical motion of the unsupported sternum. Some surgeons omit the external support but the lack of paradoxical motion and the better correction of the demormity obtained by the use of the ladder more than justify the added time required to attach it.

The risk of operation is not great in spite of the fact that both pleurae, the pericardium, and, occasionally, the peritoneum are exposed. There have been no fatalities in the 42 cases that form the basis for this discussion nor in the 27 cases mentioned by Brown.[7] Infection is likewise unusual. The most frequent complication is accidental pneumothorax and this can easily be relieved. The patients are usually out of bed on the second or third day after operation and can be discharged after the ladder has been removed. In the hands of a surgeon experienced in thoracic procedures the operation should have no hazards.

The end results are excellent from the functional standpoint. From the physical standpoint, the deformity can be almost completely corrected by the radical operation up to the age of 5 years. After that age the result may not be as good but, except for one failure, at least 75 per cent correction has been obtained in all cases and in most the correction has been 90 per cent or better. When the simple operation has been employed in infants of about one year of age the results have been good. At an older age the functional result is good with the simple operation, but the funnel remains only partially corrected and in 2 cases reoperation, using the radical operation, has been necessary.

SUMMARY

Funnel chest is a congenital deformity with familial tendencies which is characterized by a funnel-shaped deformity of the anterior chest wall. It has serious physical, physiologic, and psychologic effects. The treatment is surgical, the results are uniformly good, and almost complete correction can be obtained if the operation is performed before the age of 5 years.

REFERENCES

1. Bauhinus, J.: Quoted by Brown, A. L. (Ref. 3 below.)
2. Ochsner, A., and DeBakey, M.: Chonechondrosternon: Report of a Case and Review of the Literature, J. Thoracic Surg. 8: 469, 1939.
3. Brown, A. L.: Pectus Excavatum (Funnel Chest), J. Thoracic Surg. 9: 164, 1939.
4. Holinger, P. H.: Discussion of Paper by Lester, C. W. (Ref. 6 below.)
5. Lester, C. W.: Surgical Treatment of Funnel Chest, Ann. Surg. 123: 1003, 1946.
6. Lester, C. W.: Funnel Chest and Allied Deformities of the Thoracic Cage, J. Thoracic Surg. 19: 507, 1950.
7. Brown, A. L.: Discussion of Paper by Lester, C. W. (Ref. 6 above.)

THE VARIABILITY OF THE ELECTROCARDIOGRAM IN CONGENITAL TRICUSPID ATRESIA

IRVING G. KROOP, M.D.,* AND ARTHUR GRISHMAN, M.D.
NEW YORK, N. Y.

LEFT axis deviation without bundle branch block in the presence of congenital heart disease with cyanosis should suggest the diagnosis of congenital tricuspid atresia. According to Taussig,[1] tricuspid atresia is the only malformation of the cyanotic group to cause left axis deviation; a "balanced" electrocardiogram, however, may be obtained occasionally in very young infants with tricuspid atresia, instead of the usual left axis deviation. Brown[2] also states, without citing examples, that the electrocardiogram in tricuspid atresia may show a normal axis. From a review of the literature, Edwards and Burchell[3] conclude that left axis deviation is an important aid in the clinical diagnosis of tricuspid atresia, but that it is not pathognomonic. Schnitker[4] and Mannheimer,[5] like Edwards and Burchell, do not consider left axis deviation as invariably characteristic of tricuspid atresia because left axis deviation may be present in cyanotic congenital heart disease other than tricuspid atresia.

In this article, we present the electrocardiographic findings in six patients with congenital tricuspid atresia. The diagnosis in five cases is verified by autopsy, and in the sixth (R. R.) by angiocardiography. Our results demonstrate the variability of the electrocardiographic findings and include two cases of tricuspid atresia without left axis deviation.

MATERIALS AND RESULTS

CASE 1.—M. D.,[6] a 10½-month-old female infant. Findings were: tricuspid atresia without transposition of the great vessels; bicuspid stenotic pulmonic valve; hypoplasia of pulmonary artery; patent ductus arteriosus; persistent ostium secundum; small interventricular septal defect; hypoplasia of right ventricle; and hypertrophied left ventricle.

The axis deviation is unusual. S_1 is present and is equal in amplitude to R_1. S_3 is greater than R_3 and R'_3, but R_2 is greater than R_1 and R_3. P_2 is tall and peaked. CF_4 shows a very deep S wave. There is no evidence from the standard leads and from CF_4 for a diagnosis of left ventricular hypertrophy (Fig. 1).

CASE 2.—C. C.,[7] an 8-month-old male infant. Findings were: tricuspid atresia with complete transposition of the great vessels; dilatation of the pulmonary artery; hypoplasia of the descending aorta; persistent ostium secundum; interventricular septal defect; hypoplastic right ventricle; and hypertrophied left ventricle.

From the Cardiographic Department and the Cardiovascular Research Group, the Mount Sinai Hospital, New York.
*Sara Welt and Dazian Fellow in Medicine; the Mount Sinai Hospital, New York.
Present address: Department of Cardiology, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y.

There is left axis deviation. A small S_1 is present. S_2 and S_3 are deep. P_1, P_2, and P_3 are tall and peaked. The QRS in CF_4 is normal and consists of a tall R and small S wave. There is no evidence from the standard leads and from CF_4 for a diagnosis of left ventricular hypertrophy.

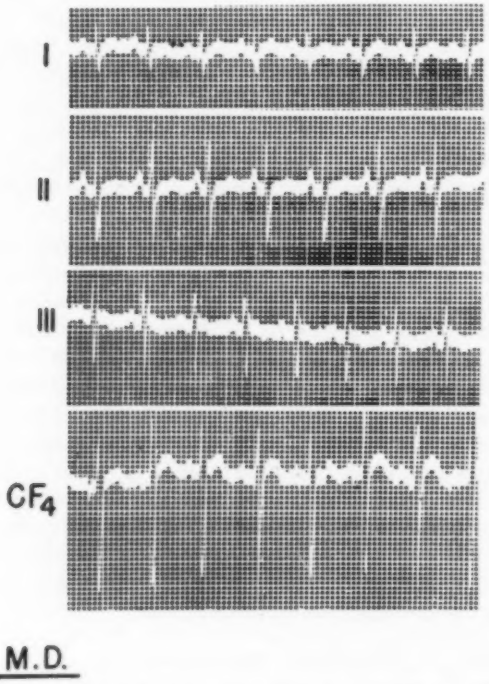


Fig. 1.—Unusual axis deviation. Deep S_1 and S_2. Deep S_3 greater than R_3 and R'_3. Small R, deep S pattern in CF_4. P_2 is prominent. No evidence for a diagnosis of left ventricular hypertrophy.

CASE 3.—F. R.,[8] a 6-month-old female infant. Findings were: tricuspid atresia with transposition of the great vessels; dilatation of the pulmonary artery; coarctation of the aorta; patent ductus arteriosus; persistent ostium primum; interventricular septal defect; tricuspid mitral valve; hypoplastic right ventricle; and hypertrophied left ventricle.

The electrical axis is unusual. A small Q_1 and S_1 are present. The QRS in Lead III is biphasic, the major positive deflection (R-R′) being greater than the S wave. P_2 is tall and peaked. The QRS in CF_4 is biphasic and of high voltage. T_2 and T_3 are inverted. Neither the standard leads nor CF_4 suggest left ventricular hypertrophy (Fig. 2).

CASE 4.—R. B.,[8] a 6-month-old male infant. Findings were: tricuspid atresia without transposition of the great vessels; hypoplastic pulmonic valve and pulmonary artery; dilatation of the ascending aorta and arch; persistent ostium secundum; interventricular septal defect; hypoplastic right ventricle; and hypertrophied left ventricle.

Left axis deviation is present. T_1 is biphasic. S_1 is absent. RS-T_1 and T_2 are slightly depressed. There is a small Q and tall R in aV_L and a small R and deep S in aV_F. aV_R consists of a deep Q and small R of low voltage. There are biphasic QRS complexes of high voltage from V_1 to V_6. Over the right midscapula and right posterior axillary line, the QRS complex resembles that seen over the surface of the left ventricle. Over the right anterior axillary line, there is a biphasic QRS complex similar to those over the precordium from V_1 to V_6. P_2 is tall and peaked.

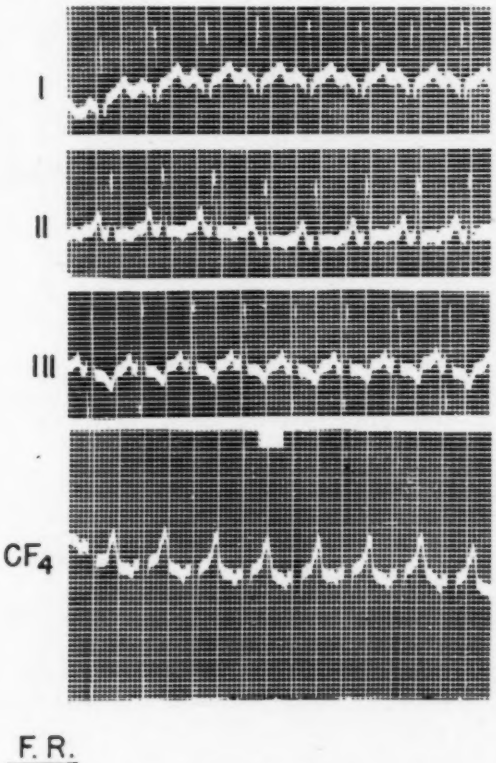


Fig. 2.—Unusual axis deviation. Biphasic QRS in Lead III. Major positive deflection (R-R') is greater than S_2. P_2 is prominent. QRS in CF_4 is biphasic and of high voltage. No evidence for a diagnosis of left ventricular hypertrophy.

There is no distinct evidence for a diagnosis of left ventricular hypertrophy. The complexes over the right midscapula and right posterior axillary line indicate extreme clockwise rotation along the vertical axis. The RS-T and T wave changes are in all likelihood due to digitalis (Fig. 3).

CASE 5.—R. R.,[9] a 5-year-old boy. Findings were: tricuspid atresia with transposition of the great vessels; hypoplasia of the pulmonary artery and the right ventricle; hypertrophied left ventricle; and interarterial and interventricular septal defect.

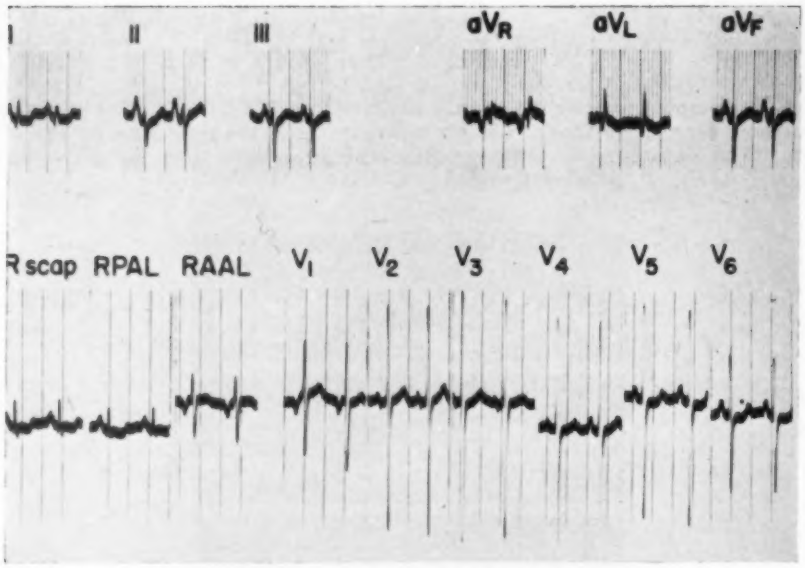


Fig. 3.—Left axis deviation. The tall R in aV_L and deep S in aV_F determine the left axis deviation. The small Q, tall R, small S, complex over the right chest posteriorly indicates marked clockwise rotation. P_2 is prominent. There is no evidence for a diagnosis of left ventricular hypertrophy. The RS-T and T wave changes are in all likelihood due to digitalis. (RScap = right scapula: RPAL = Right posterior axillary line; RAAL = Right anterior axillary line.)

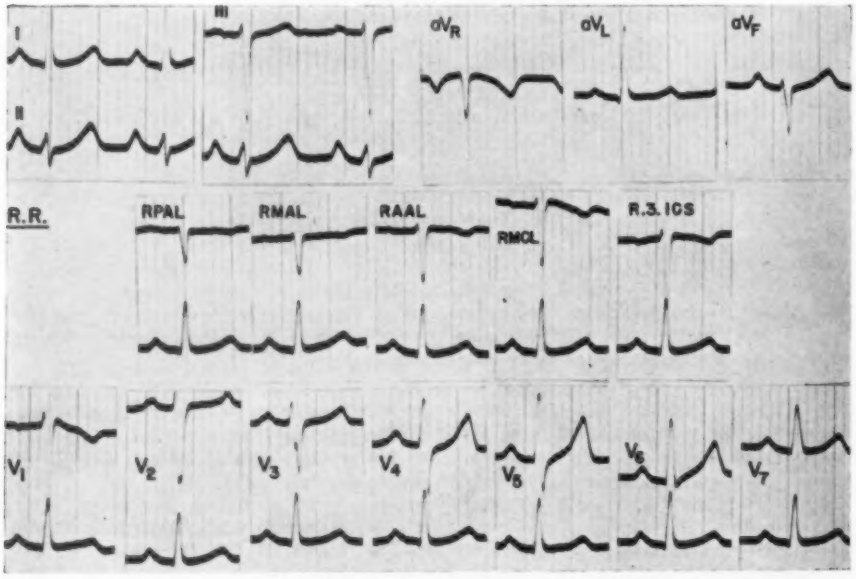


Fig. 4.—Left axis deviation. Tall R in aV_L and deep S in aV_F determines the left axis deviation. Precordial leads are normal. There is no evidence for a diagnosis of left ventricular hypertrophy.

TABLE I

NAME	AGE	TRANSPOSITION OF GREAT VESSELS	P WAVE	AXIS DEVIATION	S_1	Q_1	PRECORDIAL LEADS	EXTREMITY LEADS	EVIDENCE FOR LEFT VENTRICULAR HYPERTROPHY	COMMENT*
D. B.	2 wk.	Without	P_2 tall and peaked	Left	Absent	Small	Normal	Tall Positive R in aV_L	None	Positivity in aV_L determines LAD
R. B.	6 mo.	Without	P_2 tall and peaked	Left	Absent	Small	Biphasic QRS of high voltage	Tall Positive R in aV_L	None	Positivity in aV_L determines LAD; precordial leads indicate rotation
F. R.	6 mo.	With	P_2 tall and peaked	Unusual	Small	Small	CF_4: biphasic QRS of high voltage	—	None	Peculiar biphasic QRS in Lead III indicates rotation
C. C.	8 mo.	With	P_1, P_2, and P_3 tall and peaked	Left	Small	Absent	CF_4: tall R, small S	—	None	P wave changes are marked
M. D.	10½ mo.	Without	P_2 tall	Unusual	Deep S_1 equals R_1	Absent	CF_4: small R, deep S	—	None	Standard and precordial leads indicate rotation
R. R.	5 yr.	With	P_2 tall	Left	Absent	Small	Normal	Tall Positive R in aV_L	None	Positivity in aV_L determines LAD

*LAD = left axis deviation.

There is left axis deviation. A small Q_1 is present. S_1 is absent. Lead aV_R is negative. aV_L shows a small Q and a tall R pattern and aV_F, a small R, deep S pattern. P_2 is prominent. The progression of patterns from the right precordium to the left precordium is normal. There is no evidence for a diagnosis of left ventricular hypertrophy (Fig. 4).

CASE 6.—D. B., a 2-week-old male infant. Findings were: tricuspid atresia without transposition of the great vessels; bicuspid pulmonic valve; normal pulmonary artery; small interatrial and interventricular septal defects; hypoplastic right ventricle; and hypertrophied left ventricle.

There is left axis deviation. A small Q_1 is present. S_1 is absent. T_1 is low. Lead aV_R is negative. There is a small Q, tall R pattern in aV_L and a negative QRS complex in aV_F. P_2 is peaked and prominent. The precordial leads show the normal progression from the small R deep S pattern over V_1 to the small Q, tall R, small S pattern over V_5. There is little evidence for a diagnosis of left ventricular hypertrophy.

DISCUSSION

Left axis deviation is a frequent finding and therefore an important aid in the diagnosis of tricuspid atresia. Left axis deviation may be present as early as 2 weeks of age (D. B.). Age in itself is therefore not a factor in determining left axis deviation in tricuspid atresia. The presence or absence of transposition of the great vessels is also not a determining factor. In our cases (Table I), left axis deviation is present in subjects with and without transposition of the great vessels.

Electrocardiographically, the factor which determines left axis deviation in the standard leads is the positivity in aV_L (tall R) and the negativity in aV_F (deep S) (Cases D. B., R. B., and R. R.). Most interesting is the absence of electrocardiographic evidence of left ventricular hypertrophy in the unipolar limb and precordial leads, despite the presence of a dilated and markedly hypertrophied left ventricle and a diminutive hypoplastic right ventricle.

Left axis deviation may be absent in cases of tricuspid atresia. In two of our patients, one with and the other without transposition of the great vessels, an unusual axis deviation is present. The presence or absence of transposition of the great vessels is obviously not a factor in determining the unusual axis. Precordial leads may present evidence of unusual cardiac rotation.

The P waves are tall and peaked in all our cases, and of unusually high voltage in all the standard leads in one case (C. C.). The prominent P waves are associated with the atrial enlargement and hypertrophy which is present in tricuspid atresia. By its position and relation to the diaphragm, and by its effect on the rotation of the enlarged left ventricle, the right atrium may be an important determinant of the axis deviation and the electrocardiographic pattern in the precordial leads (Fig. 3).

CONCLUSIONS

1. Left axis deviation may be absent in some cases of congenital tricuspid atresia.

2. The absence of left axis deviation should not rule out the diagnosis of congenital tricuspid atresia.

3. The positivity in aV_L and negativity in aV_F determine the left axis deviation in the standard leads. Neither age nor the presence or absence of transposition of the great vessels is a factor.

4. Despite the presence of left ventricular hypertrophy and a hypoplastic right ventricle in our patients with tricuspid atresia, no definite electrocardiographic evidence of left ventricular hypertrophy is seen.

5. Because of its marked enlargement and diaphragmatic position, the right atrium may strongly affect the potential distribution to the chest by marked rotation and displacement of the left ventricle.

REFERENCES

1. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund, p. 86.
2. Brown, J. W.: Congenital Heart Disease, London, 1939, Staples Press Ltd., p. 166.
3. Edwards, J. E., and Burchell, H. B.: Congenital Tricuspid Atresia: A Classification, M. Clin. North America **33**: 1177-1196, 1949.
4. Schnitker, M. A.: The Electrocardiogram in Congenital Cardiac Disease: A Study of 109 Cases, 106 With Autopsy, Cambridge, Mass., 1940, Harvard University Press, p. 111.
5. Mannheimer, E.: Morbus Caeruleus: An Analysis of 114 Cases of Congenital Heart Disease With Cyanosis, New York, 1949, S. Karger, p. 162.

Cases reported in detail by:

6. Holder, E. C., and Pick, J.: Congenital Heart Disease: Atresia of Tricuspid Orifice, Hypoplasia of the Right Ventricle, Septal Defects, and Patent Ductus Arteriosus, J. Tech. Methods **19**: 135-147, 1939.
7. Robinson, A., and Howard, J. E.: Atresia of the Tricuspid Valve With Transposition of the Great Vessels, Am. J. Dis. Child. **75**: 575-581, 1948.
8. Kroop, I. G.: Congenital Tricuspid Atresia. (To be published.)
9. Blumenthal, S., and Brahms, S. A.: Congenital Tricuspid Atresia With Transportation of the Great Vessels. (To be published.)

A CLINICAL TRIAL WITH CHLOROMYCETIN IN SHIGELLA DYSENTERIAE (SONNE)

A Report of Three Cases

Milton M. Mazursky, M.D.
Akron, Ohio

MULTIPLE reports have appeared during the past ten years which have firmly established sulfanilamide derivatives as the drugs of choice in the treatment of dysentery caused by the Shigella organisms.

It had always been the prevailing medical thought that a drug, in order to be effective against the Shigella bacilli, would have to act locally in the gastrointestinal tract.

Consequently, when it was shown in 1940[1] that sulfaguanadine was bacteriostatic towards these intestinal pathogens, and in addition, poorly absorbed from the enteric tract, clinical investigations followed[2-4] which led to the recognition of sulfaguanadine therapy as the treatment of choice.

In 1942 and 1943, other reports such as that by Smyth, Finkelstein, and associates[5] appeared which suggested that succinylsulfathiazole, another poorly absorbed sulfonamide, was to be preferred to sulfaguanadine in the treatment of bacillary dysentery.

It was largely through the papers published by Hardy and his associates in 1943 and 1946,[6-8] that readily absorbed sulfonamides, sulfadiazine in particular, have supplanted the poorly absorbed derivatives previously mentioned, in Shigella dysentery treatment.

They demonstrated first, through their cultural data, that sulfadiazine had the greatest bacteriostatic action on Shigella organisms, and secondly, that high levels of sulfadiazine and Sulfapyrazine were present in the gastrointestinal tract due chiefly to incomplete absorption of these drugs.

In addition, the absorbed circulating sulfonamide reached bacilli hidden in the crypts, growing in or on the mucous membranes, or present in the mesenteric lymph nodes.

Despite the acceptance of sulfanilamide derivatives as *the* treatment for Shigella dysentery, the use of these drugs has certain drawbacks and limitations:

1) There are those patients who develop allergic manifestations with the use of sulfonamide drugs, necessitating the discontinuation of therapy.

2) The use of these drugs carries with it the possibility of drug toxicity: fever, anemia, vomiting, skin rash, crystalluria, and renal obstruction.

3) Sulfonamide resistant strains of Shigella may be present resulting in relapses, failures, and the development of the carrier state.

4) In those cases where dehydration secondary to the diarrhea has occurred, it is dangerous to initiate sulfa therapy (using either the poorly or more readily

From the Children's Hospital, Akron, Ohio.

absorbed derivatives) until hydration has been restored. In infants and young children particularly, this may delay the introduction of chemotherapy for twenty-four to thirty-six hours.

Because of the aforementioned reasons, it would be desirable to have another chemotherapeutic agent available that could be used instead of or in conjunction with the sulfonamide derivatives.

The following case reports suggest that Chloromycetin may be that agent.

We admit that a definite conclusion is certainly not warranted from the material presented, but we hope that our report may serve as a springboard for further extensive investigation.

CASE REPORTS

CASE 1.—L. R., a 9-year-old white female child, was admitted to the hospital on Nov. 15, 1949, at 10 P.M. with the chief complaint of pain in the abdomen which had started seven hours before admission. The pain was described as having been dull, inconstant, and located above and to the right of the umbilicus. Three hours after its onset, the pain had disappeared. Thereafter, the patient had become feverish, nauseated, and had vomited food and mucus several times. There had been two bowel movements that day which the girl could describe only as "loose."

The family history, and the patient's birth, developmental, and past histories were noncontributory except that this was about the fourth episode of the "runs" she had had that year.

Physical examination at the time of admission revealed an acutely ill-appearing youngster, yet with no positive physical findings except for a temperature of 101.8° F.

A cell blood count done on admission showed 21,800 white blood cells with 86 per cent neutrophils of which 6 per cent were stab forms. The red blood count and hemoglobin were normal. A urinalysis done at the same time was normal.

The patient was put on clear liquids, Kaopectate, bismuth subcarbonate, and was given one dose of Crysticillin. By 8 A.M. the morning following admission, she had had six liquid green stools, several containing particles of blood-tinged mucus, and had begun to complain of periumbilical pain. Five reddish-brown liquid stools were passed on November 16, but the patient had no complaints, took liquids well, and did not vomit. Her temperature had fallen to normal and remained so during the rest of her hospital stay. Proctoscopy, performed on November 17, showed multiple small hemorrhages of the mucosa. During the next thirty-six hours, the girl continued to have multiple green liquid stools.

At this time, four reports of stool cultures taken on November 16 and 17 were received. Three of these were positive for *Shigella sonne*, and in addition, all were positive for blood, negative for ova and parasites, and two were positive for pus.

Consequently, on the evening of November 18, approximately 72 hours after admission, the patient was started on Chloromycetin. She was given 60 mg. per kilogram of body weight divided into three equal doses given at hourly intervals, followed by 30 mg. per kilogram of body weight per 24 hours divided into 6 equal doses given every four hours.

Following the institution of therapy the youngster had no bowel movement for thirty-six hours. At this time, a passed stool was formed and brown. The patient then had only two other bowel movements, both well formed, during her remaining time in the hospital; she had no complaints; and was discharged on November 25.

Chloromycetin in the above dosage was given for four days, being discontinued on November 22. Kaopectate and the bismuth had been stopped 24 hours before Chloromycetin was started.

Five stool cultures were obtained on November 21, 22, 23, and 24, and all were negative for pathogens, pus, blood, ova, and parasites. A repeat blood count and urinalysis on November 20 were normal.

CASE 2.—R. M., a 6-year-old white male child, was admitted at 3 P.M. on Oct. 24, 1949, with the history of red urine of three days' duration accompanied by fever, chills, frequency, and nausea. There had been no vomiting, headache, or any swelling of parts of the body. The patient had received no medication or partaken of any food which could have accounted for the red urine, nor was there any history of trauma.

The family history, and the patient's birth, developmental, and past histories were noncontributory.

Physical examination at the time of admission revealed an acutely ill looking, moderately dehydrated boy. Otherwise, no positive physical signs were found. His temperature and blood pressure were normal.

Urinalysis the day of admission and daily thereafter until November 2 were always normal. A cell blood count on admission showed a normal red blood count and hemoglobin, and a white blood count of 14,000 with 40 per cent lymphocytes, 52 per cent polymorphonuclears of which 4 per cent were stab forms. Nonprotein nitrogen, blood urea nitrogen, and creatinine determinations done that same day were also normal. A normal flat plate of the abdomen was obtained on October 26.

For four days following admission (until October 28), the patient averaged two liquid to semiliquid stools daily. These were brown, contained no gross blood, and several contained much mucus. The patient was receiving only kaopectate and a soft to regular diet. He had no complaints. During his entire hospitalization, the boy remained afebrile.

On the evening of October 28, the culture report on a stool specimen of October 26 was received which was positive for *Shigella sonne*, pus, blood, and negative for ova and parasites. No other specimens had been sent to the laboratory for examination.

As a result of the stool report, the patient was immediately started on Chloromycetin (approximately 100 hours after admission). The dosage and schedule of Chloromycetin employed was the same as in Case 1.

Four hours after the initiation of therapy, the patient had a soft dark-brown stool. Thereafter, he averaged one formed brown stool daily until his discharge on November 6.

Chloromycetin was given for 6 days, being discontinued on November 3. Kaopectate had been discontinued 12 hours before chemotherapy was started.

Five stool cultures were obtained on November 2, 3, 4, 5, and 6. All were negative for pathogens, pus, blood, ova, and parasites.

The cause for the red urine was never determined.

CASE 3.—J. P., a 6½-year-old white female child, was seen in our emergency room at 7 P.M. on Nov. 4, 1949, cyanotic and convulsing. This had been the fourth similar episode that day.

The patient had a definite history of birth injury. She had had repeated convulsions from infancy up until 3 years of age. From then on until the present occurrences, convulsions had been absent. From the description of the convulsions by the parents, they seemed to fit the grand mal type. The girl's developmental history revealed that she had been slow in learning to walk, talk, and in developing habits.

The family history was noncontributory.

No mention of any gastrointestinal symptoms in relation to the present illness was made by the parents; nor were any other pertinent facts obtained from the history.

Physical examination on admission after the patient stopped convulsing was completely normal except for a temperature of 103° F. The diagnosis of cerebral dysfunction secondary to a birth injury was entertained.

A cell blood count done the morning after admission showed a normal red blood count and hemoglobin, but the white blood count was 18,200 with 73 per cent polys of which 1 per cent were stab forms, and 25 per cent lymphocytes. A urinalysis on November 6 was normal. An electroencephalogram on November 8 was read as epilepsy associated with generalized cortical atrophy. Cortical atrophy was also found by routine pneumo-encephalographic studies on November 12.

On admission the child was placed on a liquid-to-soft diet and on phenobarbital. In the 12 hours following hospitalization, the patient had seven liquid, brown stools, several of which contained blood flecks and mucus. During the next four days, until the morning of November 9, the girl had sixteen stools, fourteen of which were liquid or semiliquid, the other two being soft. Many of these stools also contained blood and mucus. The girl's temperature meanwhile ranged between 100° and 100.5° F. She didn't feel particularly ill, and she ate fairly well. No specific therapy was given.

On the morning of November 9, we received culture reports on stool specimens taken November 5, 6, and 7. Two of these were positive for *Shigella sonne*, and all were negative for pus, blood, ova, and parasites.

Accordingly, Chloromycetin was started immediately (about 108 hours after admission) in the dosage and on the schedule previously described.

A small brown formed stool was passed four and one-half hours after starting the drug, and thereafter, the youngster averaged one formed brown stool daily until her discharge on November 15.

Chloromycetin was continued for five days, being omitted after November 14. During the period chemotherapy was being given, the patient ran a spiking temperature to 103.5° F. This rapidly fell to normal after the drug was discontinued.

Stool cultures were obtained on November 10, 11, and 14. These were all negative for pathogens.

A cell blood count on November 14 was essentially normal.

COMMENT

Unfortunately, long term follow-up of our cases including periodic stool cultures was not possible under our hospital setup. However, the rapid change in the character of the stools and the consistently negative stool cultures obtained during and shortly after therapy in all three cases, are promising highlights.

SUMMARY

1. The limitations and drawbacks of sulfa therapy in shigellosis (though this is the therapy of choice) are presented.

2. Three cases of *Shigella sonne* dysentery treated with Chloromycetin are presented.

3. The results obtained clinically were highly satisfactory, suggesting that further investigation be undertaken to determine definitely the status of the drug in the treatment of the disease.

REFERENCES

1. Marshall, E. K., Jr., Bratton, A. C., White, H. J., and Litchfield, J. T., Jr.: Sulfaguanadine—A Chemotherapeutic Agent for Intestinal Infections, Bull. Johns Hopkins Hosp. **67**: 163, 1940.
2. Lyon, G. M.: Chemotherapy in Acute Bacillary Dysentery, West Virginia M. J. **37**: 54, 1941.
3. Rantz, L. A., and Kirby, W. M.: The Use of Sulfaguanadine in the Treatment of Dysentery Carriers, J. A. M. A. **118**: 15, 1942.
4. Marshall, E. K., Jr., Bratton, A. C., Edwards, L. B., and Walker, E.: Sulfaguanadine in the Treatment of Acute Bacillary Dysentery in Children, Bull. Johns Hopkins Hosp. **68**: 94, 1941.
5. Smyth, C. J., Finkelstein, M. B., Gould, S. E., Koppe, T. M., and Leeder F. S.: Acute Bacillary Dysentery (Flexner) Treatment With Sulfaguanadine and Succinylsulfathiazole, J. A. M. A. **121**: 17, 1943.
6. Hardy, A. V., and Cummins, S. D.: Studies of the Acute Diarrheal Diseases; A Preliminary Note on the Clinical Response to Sulfadiazine Therapy, Pub. Health Rep. **58**: 18, 1943.
7. Hardy, A. V., and Cummins, S. D.: Studies of the Acute Diarrheal Diseases; Cultural Observations on the Relative Efficacy of Sulfonamides in Shigella Dysenteriae Infections, Pub. Health Rep. **58**: 18, 1943.
8. Hardy, A. V.: The Sulfonamides in Shigellosis, Pub. Health Rep. **61**: 24, 1946.

ORTHOPEDIC TREATMENT OF THE PIGEON-TOED CHILD

WALTER SCOTT, M.D., AND CHARLES G. HUTTER, M.D.
HOLLYWOOD, CALIF.

THE child with a pigeon-toed gait poses a real problem for both the pediatrician and the orthopedic surgeon, largely because of a misconception regarding the prevalence and importance of this deformity in adult life. There are no standards by which to determine which child requires special corrective treatment. At the present time, treatment is usually instituted only when pressure from the child's family exceeds the indifferent attitude of the doctor, and then inadequate corrective measures are frequently used. Too often the problem is dismissed with the comment, "Don't worry, he will outgrow it."

In the light of data gradually being compiled, the child's parents should be informed that approximately one per cent of the adult American population possesses this deformity, with its functional, cosmetic, and psychologic handicaps. It may be stated that two views exist concerning the correction of this condition in the growing child. One group expects spontaneous correction along with the child's growth. The other believes that only operative sectioning will correct the deformity in the severe cases. The authors wish to present a simple method of correcting this condition without exposing the child to the hazards of operation.

Pigeon-toed gait is usually due to rotational alterations in the tibia, sometimes to a deformity of the forefoot, and occasionally to an internal rotational deformity of the hip. Correction of the forefoot deformity (metatarsus varus) is a difficult one and should be included with discussions of clubbed feet. Rather than enter into such discussion, we shall confine the subject matter to the pigeon-toed gait due to rotational or torsional change in the tibia.

TIBIAL TORSION

The normal or average rotation of the adult tibia is approximately 20 degrees in an outward direction. This measurement represents the degree of external rotation which the axis of motion of the ankle joint subtends with the axis of motion of the knee joint. These joints do not have the same plane of motion. (Fig. 1.)

In a recent publication[1] we reported on the structure of the tibia at various ages. The findings indicated that internal torsion is normal in the newborn infant, and that a spontaneous external torsion amounting to 20 degrees can be expected to present itself by the end of the second year, providing there are no deterring forces present. Forces which produce external rotation of the tibia are active during the daily life of the average child, and will result in normal knee-ankle relationship, provided there are no bad postural habits to prevent this developmental change.

Several faulty habits were found to explain persistence and even increase in the deformity. First, and most important, was the sleeping position. Practically all of the children with internal torsion slept on their abdomens with the toes pointing toward each other, thus effecting an internal twisting of the tibia throughout the night. The second most prevalent factor was faulty sitting posture. One of us (C. H.) had the opportunity to observe the native Japanese, a people in whom the pigeon-toed gait is extremely common. The bulk of the Japanese population does not sit on chairs, but rather on the floor, with the feet turned inwardly under the buttocks. This postural attitude accounts for the high degree of internal torsion among the natives. Fifty American-born adults of Japanese extraction were examined, and were found comparable to the American group tested. Many of the parents of children treated for internal torsion stated that their child was often observed sitting in a similar position with the feet turned in under the buttocks. Some children both crawl and sit with their feet turned inwardly and in some cases the habit of tightly tucking in the child's bed covers presses the legs into a position of deformity during the sleeping hours.

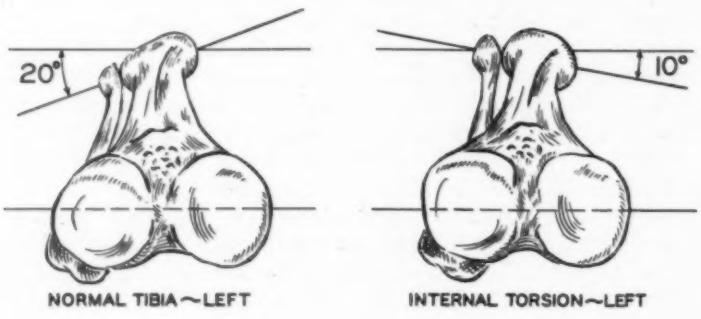


Fig. 1.—*A*, External torsion of 20 degrees is normal. *B*, Internal torsion of 30 degrees (20 plus 10 degrees).

DIAGNOSIS

The diagnosis of tibial torsion is clinically quite simple. The presenting complaints invariably are that the child "toes in" or "falls over his feet." (Fig. 2.)

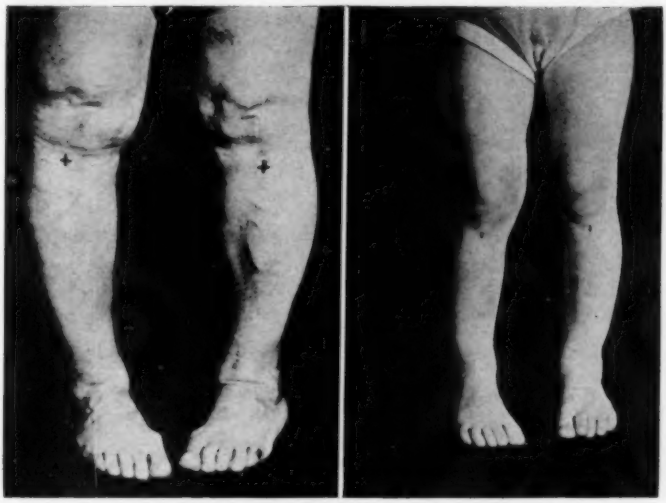
The deformity is readily demonstrated by standing the child and rotating the leg until the patella becomes centered on the anterior surface of the knee, so that it and the tibial tubercle point directly at the examiner. This may also be performed with the child lying on his back, in which case the patella should point toward the ceiling. Another method is to flex the knee to a right angle and look down the longitudinal axis of the tibia, as demonstrated in Fig. 1.

When is tibial torsion abnormal? The authors previously[1] stated that 20 degrees variation from the normal 20 degrees of external rotation might be considered within normal limits. This allows for a very wide variation of the

so-called normal. Clinically, it is very difficult to accurately measure torsional deformity in a small child, so we consider abnormality of gait combined with clinical deformity to be more important in the indication for treatment than the degree of deformity alone.

TREATMENT

Treatment in the past resolved itself into several measures, many of which are time consuming and inadequate. Derotation exercises performed by the parents at home are usually unsatisfactory, and may cause ligamentous damage. Corrective shoes and casts applied to the lower leg are ineffective in producing a twist opposite to that of the deformity unless coupled with a device which will fix the position of the pelvis. In mild cases it may be possible to augment natural forces by the application of a patch to the outer side of the sole of the shoe.



A. *B.*

Fig. 2.—*A*, A 50-year-old woman with severe internal torsion. *B*, A 3-year-old child with the same deformity.

The treatment we advocate is predicated upon the age-old observation that the growing bones respond slowly but definitely to stresses and strains exerted upon them. A strain exerted in a direction opposite to that of the deformity will effect a correction of that deformity in the subsequent growth period. The Denis-Browne splint functions most satisfactorily in this capacity. It consists of a bar fastened to the sole of each shoe and provided with a ratchet and wing nut so that each shoe may be turned inwardly or outwardly. (Fig. 3.) A "clamp on" type is manufactured by the Zimmer Company of Warsaw, Ind.

The child wears the splint during his sleeping hours, but not for the afternoon nap. At first the feet are not externally rotated, but as the child becomes accustomed to the splint, the feet are gradually externally rotated by adjusting

the position of the shoes upon the cross bar until approximately 45 degrees of external rotation is obtained. Care should be taken to align the ankles so that no varus or valgus of the ankle joints occurs. To avoid knock-knee, the bar separating the feet should be from 6 to 8 inches in length. The length of time which will be necessary to effect correction will vary according to the age of the patient and the severity of the deformity. It usually requires from three to six months, but the parents may note that the child is walking better after only one or two months of treatment.

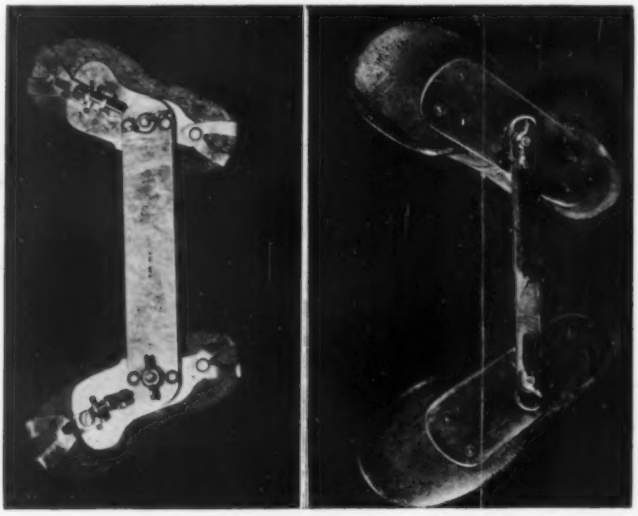


Fig. 3.—Ready-made "clamp on" type of Denis-Browne splint, manufactured by the Zimmer Company, and conventional type.

No complications of any consequence have arisen in more than 200 cases. In a few instances the child became "too nervous" to continue wearing the splint. Too rapid correction could, potentially at least, lead to stretching the ligaments about the knee joints, but in our series no such complication has arisen.

CASE REPORT

M. M., a 5-year-old boy, had always walked with a pigeon-toed gait. He frequently fell when he attempted to run, because of "stumbling over his own feet." He slept on his abdomen with the feet turned inward. At the age of 2 years, he was taken to a doctor, and special corrections for the shoes were prescribed. For three years he wore these shoe corrections without any change in the deformity.

He had always been under the care of a pediatrician, and had never been seriously ill. There was no history of rachitic disease.

Examination revealed a normal, well-developed boy with no osseous or muscular deformity except severe internal torsion of the tibiae. He walked with a pronounced pigeon-toed gait. The feet were entirely normal.

Roentgenograms and other laboratory studies were entirely negative.

Treatment consisted of wearing a Denis-Browne night splint for six months. At the end of this time, the pigeon-toed gait was entirely corrected, together with the deformity of the tibiae. (Fig. 4.) The child had no further difficulty.

Fig. 4.—Case of M. M. before and after treatment.

Fig. 5.—Marked external torsion in an 8-year-old boy.

EXTERNAL TORSION

This condition is the reverse of the internal trosion type of deformity and results in a "duck-toed" gait. Fortunately, these cases are uncommon and unless very extreme, are not cosmetically objectionable. In boys, it results in

faulty leg function, and they are unable to run with facility or to excel in the running sports. (Fig. 5.)

The treatment is the same as for internal torsion, except that the feet are held in a position of internal rotation. Everything that has been said about the pigeon-toed child may be applied to these children, remembering that the deformity is just the reverse.

SUMMARY

Children with faulty sleeping or sitting habits, which lead to twisting deformities of the lower legs, will develop a pigeon-toed gait as a result of internal torsion of the tibiae. Resolution does not occur spontaneously in these children. The deformity may be corrected by the use of a Denis-Browne night splint which holds the feet in an overcorrected position for a period of from four to six months.

The "duck-toed" gait, due to external rotation of the tibiae is discussed.

REFERENCE

1. Hutter, C. G., and Scott, Walter: Tibial Torsion, J. Bone & Joint Surg. **31A**: 511-518, 1949.

Case Reports

HIGH VENTRICULAR SEPTAL DEFECT AND SLIGHT DEXTROPOSITION OF THE AORTA (EISENMENGER COMPLEX) ASSOCIATED WITH DEFORMED AORTIC VALVE SIMULATING PATENT DUCTUS ARTERIOSUS

RACHEL ASH, M.D., AND LOIS MURPHY, M.D.
PHILADELPHIA, PA.

IN 1948 Hurst and Schemm[1] reported a case of high interventricular septal defect with slight dextroposition of the aorta and deformity of the aortic valves which presented clinical features of patent ductus arteriosus as indicated by the presence of a machinery murmur heard most intensely in the second left intercostal space. More recently, Morgan and Burchell[2] reported a case with a continuous murmur in the pulmonic area in which evidence supplied by intracardiac catheterization suggested the presence of an interventricular septal defect rather than a patent ductus. The following patient in whom an interventricular septal defect, slight dextroposition of the aorta, and deformed aortic valve were found at necropsy, also presented a continuous murmur below the left clavicle, confirmed by a phonocardiogram.

CASE REPORT

High interventricular septal defect, slight dextroposition of aorta, dilated pulmonary artery (Eisenmenger complex); deformed leaflets of aortic valve; persistent left superior vena cava opening into the coronary sinus; hypertrophy and dilatation of all cardiac chambers; atelectasis of left lung; closed ductus and foramen ovale.

This white, female infant, who was 3½ years of age at death, was born Nov. 21, 1945, the first child of young parents. There was a history of asthma and hay fever on the mother's side of the family. The mother had been in good health throughout the prenatal period. The infant was born at term, was noncyanotic, and weighed 6 pounds.

She was first seen at the age of 3 months in consultation with Dr. Thomas T. Kochenderfer of Norristown, Pa., because of a cardiac murmur noted several days previously. There was a history of failure to gain weight and of recurrent colds. Examination revealed a moderately well-nourished infant (weight, 9 pounds). There was no cyanosis or dyspnea. The heart was enlarged to percussion. No thrill was palpated. A systolic murmur audible below both clavicles and to the left of the sternum was maximum in the third intercostal space. No murmur was heard posteriorly. Fluoroscopic examination revealed definite cardiac enlargement with fullness in the pulmonic region in the anteroposterior view. In oblique views both ventricles seemed enlarged. The electrocardiogram was within normal limits for infancy presenting prominent S waves in Lead I and Q waves in Lead III. There was no axis deviation. The liver was not enlarged. A right inguinal hernia was present. Kolmer test for syphilis was negative. There were 4,050,000 erythrocytes; hemoglobin was 10 Gm.

In June, 1947, herniorrhaphy was performed uneventfully under general anesthesia.

From the Children's Hospital of Philadelphia, and the Department of Pediatrics, University of Pennsylvania Medical School.

When seen for the second time in January, 1948 (age 2 years), she was small but well formed and able to engage actively in the normal life of childhood except for a tendency to tire easily. A systolic thrill was palpable along the left side of the sternum from the second intercostal space downward, best felt in the third and fourth intercostal spaces. A loud systolic murmur heard throughout the chest was maximum to the left of the sternum in the third and fourth

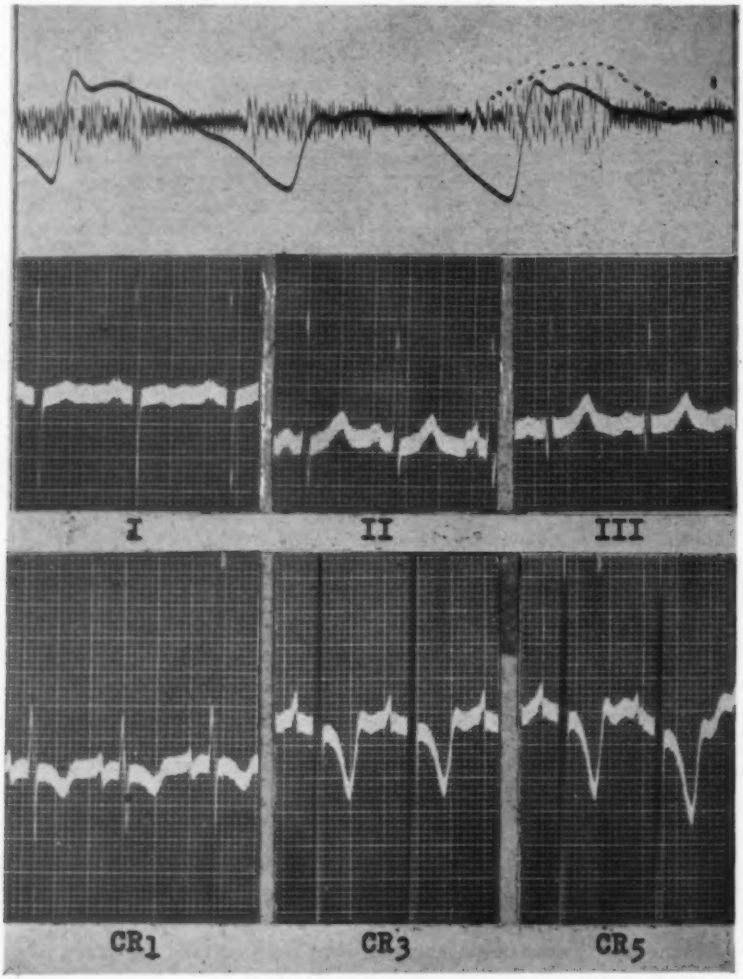


Fig. 1.—Phonocardiogram taken from the second left intercostal space of the patient; together with electrocardiogram taken April 30, 1949. Standard limb leads and precordial leads are appropriately designated. The sound tracing was taken in conjunction with a graphic record of the radial pulse. The time of systolic accentuation varies in individual cycles. The third cycle represents a murmur crescendo in systole and decrescendo in diastole similar to the murmur associated with patent ductus. (Fig. 6.) In leads CR_1 and CR_5 of the electrocardiogram the poorly visualized S waves are of greatly increased amplitude. The R waves are of equally high amplitude in CR_1, but cannot be seen with certainty in CR_5.

intercostal areas. No diastolic murmur was heard in any area. The blood pressure was 80/60. Both ventricles and the left atrium were enlarged. The esophagus was deviated posteriorly in the region of the left atrium but not displaced to the right. Shadows in the hilar areas were prominent. A diagnosis of interventricular septal defect was made.

In December, 1948, she was admitted to the Children's Hospital with severe asthmatic bronchitis associated with heart failure evidenced by dyspnea and enlargement of the liver which persisted after the asthma had subsided and which disappeared after digitalization. During this admission a rumbling, continuous murmur became audible below the left clavicle resembling the machinery murmur of a patent ductus arteriosus. (Fig. 1.) The systolic thrill and murmur previously noted were still present, maximum between the third and fifth intercostal spaces to the left of the sternum. On December 30, capillary and Corrigan pulses were noted. The blood pressure was 110/40-0 in the left arm; 140/20 in the left leg. Roentgenograms showed a greater degree of cardiac enlargement than had been noted previously. (Fig. 2.) The electrocardiogram showed no essential change in comparison with previous tracings. The T waves were inverted in precordial leads CR_1, CR_3, and CR_5. It was felt probable that in addition to an interventricular septal defect a patent ductus arteriosus was also present.

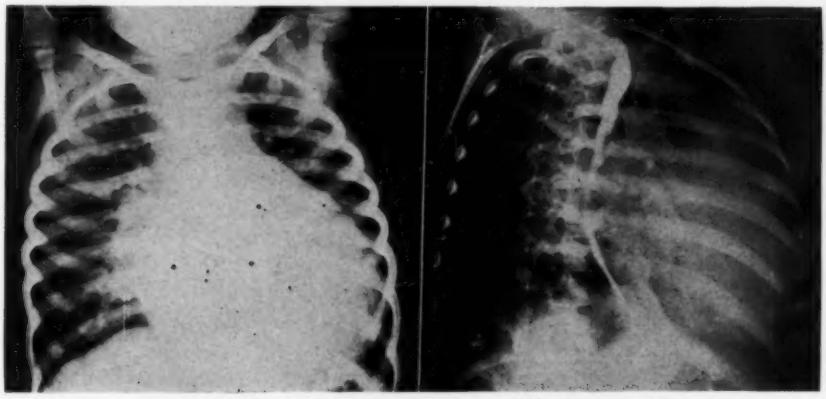


Fig. 2.—Anteroposterior and right oblique roentgenograms of the chest taken December, 1948. There is marked cardiac enlargement to the left and downward in the anteroposterior view with fulness in the pulmonary area and prominence of the vascular shadows in the right hilar region. In the right oblique view the esophagus is compressed and projected posteriorly by the greatly enlarged left atrium.

From this time on her course was progressively downhill. Despite the use of prophylactic doses of sulfamerazine or penicillin she suffered from a series of upper-respiratory infections, each of which initiated an attack of asthmatic bronchitis. The heart failure was increasingly difficult to control. She was twice readmitted in acute congestive failure presenting subcutaneous edema and pleural effusion which disappeared after treatment with xanthine and mercurial diuretics. A diagnosis of atelectasis of the left lung was made during the second admission. Bronchoscopy revealed constriction of the left bronchus presumably due to compression by the greatly enlarged heart. The continuous murmur below the left clavicle was heard inconstantly. It usually disappeared during attacks of acute failure but could be heard without difficulty during periods of improvement. At no time was a diastolic blow heard to the left of

the sternum or below the right clavicle. The wide pulse pressure and capillary pulse disappeared, the blood pressure in the last two months of life being 90/60-50. During the terminal two months she was maintained on digitalis, but was dyspneic at rest. No cyanosis was present.

In the hope that perhaps the patent ductus rather than the interventricular septal defect was the major factor in the production of cardiac failure, it was decided to risk operation. On May 31, 1949, exploratory thoracotomy was performed. The patient was anesthetized in the supine position. When turned to the left lateral position, respirations ceased and cardiac sounds became inaudible. The chest was opened rapidly and cardiac rhythm was restored by massaging the heart. An unsuccessful effort was made to locate a patent ductus. It was necessary to employ repeated cardiac massage together with intracardiac injections of adrenaline. When it became obvious that cardiac function could not be maintained in this fashion, the thoracic cavity was closed. The heart beat had ceased before closure was complete.

Fig. 3.—Anterior view of the heart and lungs. Marked cardiac hypertrophy; complete atelectasis of the left lung; pulmonary artery larger than aorta. *T* indicates trachea; *A*, aorta; *P*, pulmonary artery; *R. V.*, right ventricle which had previously been cut open for inspection of the interior.

Necropsy revealed significant findings only in the heart and lungs. (Figs. 3, 4, 5.) The heart weighed 180 grams and appeared many times the normal size. A large left superior vena cava was present, the right superior vena cava being very small. An enlarged pulmonary artery arose from its usual position anteriorly and to the right. Its diameter as it emerged from the ventricle was 1.9 cm. and at its division into the two main branches, 2.1 cm. The aorta, which was smaller than the pulmonary artery, arose anteriorly and slightly dextroposed. Its diameter was 1.1 cm. at its origin and 1.4 cm. at the level of the ligament arteriosum. The descending aorta had been displaced to the right by the hypertrophied left ventricle.

The right atrium was dilated and hypertrophied. The right superior and inferior venae cavae entered this chamber in the usual fashion. A large left superior vena cava coursed obliquely to the posterior wall of the left atrium, and emptied into the coronary sinus. The orifice of the coronary sinus was widely dilated. (Fig. 4.) Its diameter measured 1.5 cm., in comparison with a diameter of 0.4 cm. at the point of entry of the right superior vena cava and

Fig. 4.—The anterior cusp of the tricuspid valve is retracted to reveal the interventricular septal defect as it is viewed from the right ventricle with the right anterior and the posterior cusps of the aortic valve protruding through the defect. The white arrows point to the interventricular septal defect. *C. S.* indicates orifice of the dilated coronary sinus in the right atrium; *R.*, right anterior aortic cusp; *P.*, posterior aortic cusp; *P. M.*, papillary muscle to which anterior cusp of tricuspid valve is attached; *R. Au.*, right atrium.

Fig. 5.—Opened aortic valve viewed from the interior of the left ventricle. The white arrows point to the interventricular septal defect. *L. A.* indicates normal left anterior cusp; *R. A.*, right anterior cusp; *P.*, posterior cusp. Both of the latter cusps are thickened and sacculated.

0.9 cm. at the point of entry of the inferior vena cava. The foramen ovale was closed. The right ventricle was hypertrophied, particularly in the region of the conus. The average thickness of its wall was 0.5 cm. The tricuspid and pulmonary valves were normal in structure, the circumference being 7.2 cm. and 4.5 cm. respectively. A defect measuring 0.8 cm. in width and 1.1 cm. in length was situated at the upper margin of the interventricular septum. The distance from its anterior border to the septal margin of the anterior longitudinal sulcus was 2.3 cm. and from its posterior border to the septal margin underlying the posterior longitudinal sulcus, 2.6 cm. From the right ventricle, cusps belonging to the aortic valve could be seen projecting into the septal defect. (Fig. 4.)

The left atrium was dilated and hypertrophied. The pulmonary veins entered this chamber in the usual fashion. There was marked hypertrophy of the left ventricle, the average thickness of its wall being 1.1 cm. The mitral valve was 6.7 cm. in circumference. Its cusps were larger than those of the tricuspid valve and the papillary muscles showed a greater degree of hypertrophy, but there was no valvular deformity. The aortic valve appeared incompetent. The circumference was 4.8 cm. The left anterior cusp appeared normal and measured 1.2 cm. at its base. The base of the right anterior cusp measured 1.5 cm. Its lunula was thickened and slightly sacculated. It tended to protrude into the interventricular septal defect to a slight degree. The lunula of the posterior cusp was thickened to a greater degree and presented an aneurysmal dilatation which bulged downward and septalward into the right ventricle through the interventricular septal defect. The cusp measured 1.8 cm. at its base. The depth of the aneurysmal sac was 1.1 cm. A probe passed through the aortic valve could be directed through the interventricular septal defect along the interventricular wall of the right ventricle, indicating the presence of a slight degree of dextroposition of the aorta. The coronary arteries arose as usual behind the right and left anterior cusps. The right coronary artery was much smaller than the left; its orifice was narrowed by an atheromatous plaque in the wall of the aorta. The left lung weighed 70 grams and was entirely atelectatic. The lumen of the left main bronchus was completely obliterated by the pressure of the enlarged pulmonary artery and left atrium. The right lung was about three times the size of the atelectatic left lung. It weighed 170 grams.

COMMENT

In this report we have presented a second individual with a continuous murmur heard below the left clavicle in whom necropsy revealed a high interventricular septal defect associated with deformity of the aortic valve. In both cases, because of slight dextroposition of the aorta, a sacculated leaflet of the aortic valve could be drawn downward so as partly to close the interventricular septal defect and leave the valve incompetent. In a third living patient with a continuous murmur heard in the pulmonic area, intracardiac catheterization revealed findings suggestive of the presence of a high interventricular septal defect. The associated pulmonary hypertension noted both in diastole and in systole suggests the possibility that in this third patient the aorta may be dextroposed.

It would seem that such a combination of slightly dextroposed aorta with deformed valve and high interventricular septal defect must be taken into consideration in the differential diagnosis of persistent patency of the ductus arteriosus. How to make the clinical differentiation is a matter of practical importance. Even to the ear of a physician experienced in the diagnosis of cardiac anomalies the continuous murmur heard in the present patient was indistinguishable in character and location from the machinery murmur of a patent ductus. This impression seemed to be confirmed by a phonocardiogram

which in many of the cycles revealed crescendo systolic and decrescendo diastolic vibrations. (Fig. 1.) In the two previously reported cases (one patient still living; diagnosed by catheterization only) there was also no doubt in the minds of the attending physicians that the continuous murmur heard below the left clavicle was due to the flow of blood through a patent ductus. Hurst and Schemm's patient died suddenly during the night before a scheduled operation to close the ductus. The patient of Morgan and Burchell prior to operation was referred for catheterization of the right side of the heart merely because it seemed desirable to learn the pulmonary artery pressure and the amount of the shunt.

Gibson[3] originally described the pathognomonic murmur of a patent ductus as one which begins a little after the commencement of the first sound, filling up the short pause and continuing beyond the second sound, finally to die away

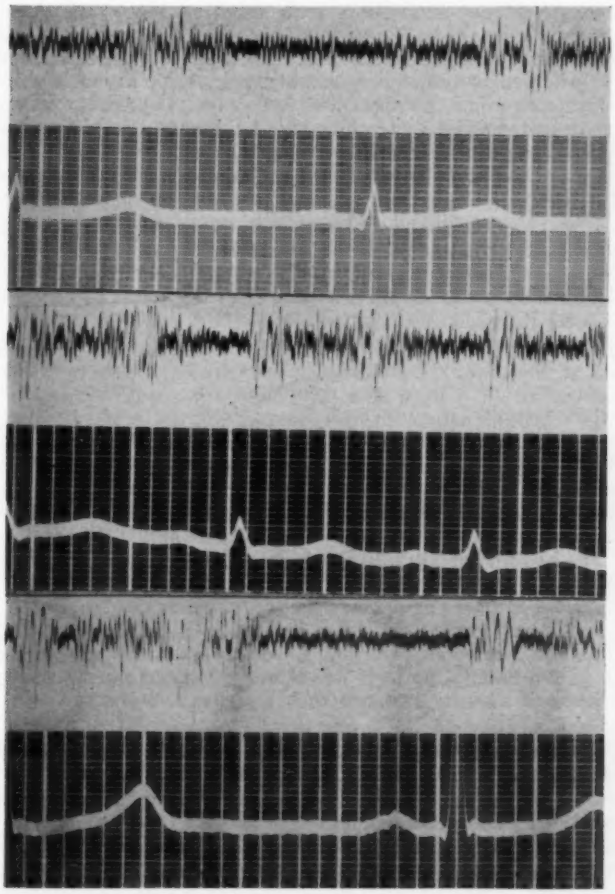


Fig. 6.—Phonocardiogram taken in the second left intercostal space from three cases of uncomplicated persistent patency of the ductus arteriosus (diagnosis proved by operation). There is variation in the time and duration of systolic accentuation in the three tracings. In general the murmur is crescendo toward the end of the systole and decrescendo in early diastole.

during the long pause. He points out that the flow through the ductus will be greatest during and immediately after ventricular systole when the aortic blood pressure is at its highest. Characteristic phonocardiograms show a low frequency murmur beginning after the onset of systole, attaining maximum amplitude at or shortly after the second sound and decreasing in amplitude during diastole. The time and duration of systolic accentuation vary to some extent in tracings from different patients and in individual cycles in the same patient. (Fig. 6.) We have seen one very atypical phonocardiogram obtained from a 4-year-old boy in whom the presence of an uncomplicated patent ductus was proved by operation. In the tracing taken from this boy a high amplitude murmur which followed the first sound had disappeared in the latter part of systole. A decrescendo murmur followed the second sound. In spite of such occasional inconsistencies, the majority of phonocardiograms derived from an individual with persistent patency of the ductus show an increase in amplitude of vibrations preceding, overriding, and following the second sound. In the phonocardiogram taken from Morgan and Burchell's patient, they point out that the systolic accentuation of the murmur precedes the upstroke of the carotid pulse wave, whereas in patients with patent ductus previously noted by them systolic accentuation had usually been found to be synchronous with the upstroke of the carotid pulse wave. The tracing pictured in their paper seems to show a diminution of the murmur toward the end of systole.

The patient described by Hurst and Schemm had been followed since the age of 16 at which time a to-and-fro murmur was best heard in the pulmonary area. Four years later for the first time a short, blowing diastolic murmur was heard in the second intercostal space to the right of the sternum, differing in quality from the diastolic murmur in the pulmonary area. No such diastolic murmur of obvious aortic origin was noted in the patients observed by us or by Morgan and Burchell.

The criticism may be made by some individuals that the existence of marked cardiac enlargement would rule out the presence of a patent ductus as an uncomplicated lesion. We have seen five individuals with excessive cardiac enlargement in whom all murmurs disappeared and the heart returned to normal size following ligation of a patent ductus. The immediate dramatic improvement in two of these children who were operated on while suffering from severe congestive failure emboldened us to consider operation in the present child. In her case, however, the diagnosis of an interventricular septal defect had been made because of the existence of a systolic murmur and thrill maximum near the xiphoid. The absence of an associated patent ductus was unexpected. In the cases described by Hurst and Schemm and by Morgan and Burchell, not only was a continuous murmur best heard in the pulmonary area, but it was in this region also that a prolonged thrill was best felt. In all three cases a wide pulse pressure was noted at some time, but since this is not an uncommon finding in association with a patent ductus it was merely accepted as confirmatory evidence of the presence of a shunt through such a lesion.

The dextroposition of the aorta in our case was so slight as to make it doubtful whether an angiogram would have revealed its presence, although it might perhaps have been helpful. Morgan and Burchell established the diagnosis in their patient by intracardiac catheterization which revealed an oxygen content in the sample of blood obtained from the outflow tract of the right ventricle nearly equal to that of arterial blood. That this was not due to gross pulmonary insufficiency associated with a patent ductus was proved by the relatively high diastolic pressure in the pulmonary artery. Whether mean pressure readings would have been of equal value in differential diagnosis is problematic. In many institutions, only mean pressure readings are available when catheteriza-

tion studies are performed. Intracardiac catheterization in our patient had been considered but was deemed unwise. The known presence of an interventricular septal defect might have made the results difficult to interpret. Moreover, catheterization would have carried almost as much risk and taken not much less time than that usually consumed by our thoracic surgeon in the performance of an operation to ligate a patent ductus. Actually, the prognosis was so hopeless that no risk short of an operation that might be successful seemed worth taking.

In the average patient with persistent patency of the ductus arteriosus, the diagnosis can be made with a high degree of accuracy by the mere detection of a characteristic machinery murmur associated with an electrocardiogram that is within normal limits. A wide pulse pressure and roentgenographic changes may supply confirmatory evidence, but are not essential to establish the diagnosis. When the heart is small or only moderately enlarged, a phonocardiogram, if characteristic, may supply an additional sense of assurance but is also not essential. Intracardiac catheterization is certainly not indicated in the average individual with a relatively small heart and a characteristic machinery murmur below the left clavicle. Before surgical treatment is recommended it would be wise, however, to refer for intracardiac catheterization individuals with marked cardiac enlargement and a continuous murmur in the pulmonary area, provided this murmur presents any abnormal features in a phonocardiogram, or is associated either with a diastolic blow of aortic insufficiency or with a thrill or systolic murmur maximum to the left of the lower sternum and indicative of the presence of an interventricular septal defect. Intracardiac pressure recordings or direct measurement of both systolic and diastolic pressures should be made; otherwise it would be impossible to differentiate between a patent ductus associated with free pulmonary regurgitation and a high interventricular septal defect of the type described in this article.

The possibility still remains, however, that a young child with greatly enlarged heart and signs suggesting the presence of a patent ductus may first be seen in a severe state of cardiac failure that fails to respond to treatment. In such a case the risk of operation may seem more advisable than the risk of catheterization, which may itself bring about a fatal issue. Two such children seen by us who proved to have a patent ductus have been successfully treated by surgery.

SUMMARY

1. A second case is presented with a continuous murmur heard in the second left intercostal space resembling the murmur of patent ductus arteriosus, in which necropsy revealed a high interventricular septal defect and slight dextroposition of the aorta (Eisenmenger complex) associated with deformity of the aortic valve.

2. Intracardiac catheterization with the use of a manometer capable of registering systolic and diastolic pressures might have established the diagnosis before operation and death.

3. Intracardiac catheterization is not recommended for individuals with continuous murmur in the pulmonary area, normal electrocardiogram, and relatively small hearts.

4. Before surgical treatment is undertaken intracardiac catheterization is recommended for individuals with a continuous murmur in the pulmonary area and marked cardiac enlargement who show abnormal features in the phonocardiogram or who present the diastolic murmur of aortic insufficiency or a systolic thrill and murmur near the xiphoid, suggesting the existence of an interventricular septal defect.

We are indebted to Dr. Irving J. Wolman for placing at our disposal the pathologic material in this case.

REFERENCES

1. Hurst, W. W., and Schemm, F. R.: High Ventricular Septal Defect With Slight Dextroposition of the Aorta (Eisenmenger Type) Which Presented the Clinical Features of Patent Ductus Arteriosus, Am. Heart J. **36**: 144, 1948.
2. Morgan, E. H., and Burchell, H. B.: Ventricular Septal Defect Simulating Patent Ductus Arteriosus, Proc. Staff Meet., Mayo Clin. **25**: 69, 1950.
3. Gibson, G. A.: Clinical Lectures on Circulatory Affections. I. Persistence of the Arterial Duct and its Diagnosis, Edinburgh M. J. n.s. **8**: 1, 1900.

ARTERIAL THROMBOSIS IN THE NEWBORN INFANT

HAROLD D. PERLMUTTER, M.D., AND DAVID H. WAGNER, M.D.
CHICAGO, ILL.

THE PRESENT literature is replete with information covering arterial embolism and thrombosis in adults, but there are very few reported cases of this type of pathology in infants.

Gangrene of the extremity due to arterial thrombosis in infants is a serious problem because the mortality rate may be high, and without previous experience in this disease process one may be led into unnecessarily radical surgery.

The first reported case of gangrene of an extremity due to arterial thrombosis was published in 1828 by Martini.[1] His patient was an 8-day-old infant who had gangrene of both extremities. The infant died on the twenty-fourth day. Ahlfeld,[2] in 1876, cited a case of gangrene of the lower extremity occurring in a 9-day-old infant. The labor in this case was long and the child was partially asphyxiated at birth. The leg was amputated and the infant died the next day.

The largest series of cases of arterial thrombosis published in the English literature, six cases, was reported by Gross[3] in 1945. An analysis of the cases studied by him and his review of the 41 cases previously published show that 4 had occurred in newborn infants and 6 had occurred on the first day of life. Twenty-one out of the 47 had occurred within the first week of life. Seventeen began within the second week and the remaining 9 cases were noted some time after the second week. Only 47 cases of arterial thrombosis in infants have therefore been reported in the literature. It is because of the rarity of this lesion and because the end result in our patient throws further light on the management of this condition, that we feel it desirable to report a case of impending gangrene of the right leg due to arterial thrombosis. This patient was observed on the Pediatric service of Dr. Ethel M. Davis at Michael Reese Hospital, in Chicago.

CASE REPORT

Baby P. R. was born at 4:18 A.M. on Aug. 26, 1946, following a short labor by his mother. The cord was wound about his neck, and his face was intensely cyanotic. There were no respirations or heart sounds audible. A tracheal catheter was passed and attempts were made at resuscitation. Thirty minutes after birth the heartbeat was palpable at the apex. Artificial respirations were continued and one hour after birth the child began to breathe. Cyanosis was moderately severe. The respirations were grunting in character. Auscultation of the lungs showed the breath sounds to be clear. The muscle tone in the right-lower extremity was noted to be poor and the question of fracture due to birth injury arose. The baby was placed in oxygen and re-examined six hours later. His condition was poor. The lungs were filled with coarse and crepitant râles throughout. Cyanosis of the face and trunk was absent but the right lower extremity was cyanotic and flaccid. Muscle twitchings were present in the arms and legs.

The infant was kept in an incubator. Examination on the next day, August 27, showed the entire body was involved in coarse tremors, sometimes reaching

From the Department of Surgery, Michael Reese Hospital, Chicago.

the convulsive state. The fontanels revealed no changes. The pupils were equal and regular. A large serpiginous cyanotic area was noted over the right buttock. The right lower extremity from the thigh-to-and-including the toes was cyanotic, mottled, and cold to the touch. No femoral pulse could be detected on the right side although it could easily be felt on the left. The right leg and foot were flaccid. The diagnosis at this time was cerebral damage, pulmonary edema, and thrombosis of the right iliac artery.

The extremity was washed carefully with alcohol and dressed aseptically. The child was placed on penicillin, 10,000 units every three hours. Continuous oxygen was instituted. Sympathetic block was considered, but because of the poor general condition of the patient, it was though to be inadvisable.

Three days later it was noted that the mottling was present as before, but the whole extremity was much warmer down to the level of the ankle. It was felt at this time that some collateral circulation had established itself in the leg. The general condition of the child was somewhat improved.

On the fifth postnatal day, the involved area over the buttock began to slough. There was no visible change in the right extremity. The temperature was 101.2° F. and respirations were 48 per minute.

On the eighth postnatal day, the sloughing over the buttock had extended. The leg remained unchanged. The child was still having occasional paroxysms of cyanosis, especially during feeding.

Between the fourteenth and seventeeth days the general condition of the patient became poor. His temperature rose to 103° F. rectally, and his respiratory rate rose to 60 per minute. His lips were cyanotic and crepitant râles were present throughout both lung fields. The ulcerated area on the buttock measured 4 to 5 inches in diameter and was covered with a dirty grayish-green exudate. There was evidence of beginning gangrenous changes in the toes.

On the twentieth day the child's general condition changed and showed definite improvement. The temperature receded. He began to eat and to gain weight, and was mentally more alert. He was still unable to move his right leg although the color of the leg and foot was improved. An x-ray of the bones of the leg on this day revealed no evidence of bony injury. The red blood count showed 5,430,000 cells with 18 Gm. Hb. It was decided to give 30 mg. of dicumarol to the infant daily. This was continued for ten days, controlled by prothrombin time readings. On the thirty-seventh day the ulcerated area on the right buttock was healing well but the toes were still dark in color. Some contracture had taken place at the knee and a spica cast was applied to correct this. After two weeks, when the child was 7 weeks old, the cast was removed and reapplied. The extremity was in good position but the leg was limp. The buttock wound was healing satisfactorily. At about 9 weeks of age the child was sent home in the cast. The tips of the toes still showed a deep bluish discoloration.

The child was seen again at 12 weeks of age and the cast removed. The wound of the buttock was healed. Now, only the tip of the fifth toe was black with dry gangrene. The rest of the extremity appeared almost normal in color and temperature. The right femoral pulse still could not be felt, and the muscles were definitely atrophied.

At fourteen weeks of age the gangrenous portion of the fifth toe sloughed off, leaving a clean, dry healing surface. Physiotherapy was started at this time. At 6 months of age motion of the right leg was poor and the muscles were atrophic. No femoral pulsation could be felt on the right side but sufficient collateral circulation had developed to satisfy the vascular requirements of the leg and foot. He was last seen in January, 1948, when he was 16 months old. At that time he was mentally and physically retarded. He was unable to raise his head, had snoring respirations, a relaxed palate, and generalized muscular

atrophy. Motion of the right leg was poor, but it was warm and the color, including the toes, was normal. A diagnosis of severe mental retardation was made and institutional care was recommended.

DISCUSSION

The etiology of gangrene of the extremities in the newborn infant is little understood. Heller and Alvari[4] divide the cases roughly into two categories: those in which gangrene seems definitely referable to pressure associated with long and difficult delivery, and those which are due to infection. However, the frequent occurrence of long and difficult labors with much trauma and the rarity of gangrene of the extremities in newborn babies suggest that there is no cause-and-effect relationship between prolonged labor with trauma and gangrene of the extremities. Nor does infection offer a very plausible explanation as the cause of gangrene in the newborn infant. Sepsis in labor is relatively common, but the babies living from such labor seldom exhibit gangrene of the extremities. Further, gangrene of the extremities occurs in cases in which neither the mother nor the baby shows any evidence of sepsis. In our case the mother was a para thirteen, who showed no evidence of infection during labor and who had a short labor with a spontaneous delivery.

Gross presents a much more plausible and attractive theory in his paper in which he points out that the majority of arterial obstructions appear within the first two or three weeks of life. This preponderance of arterial vascular accidents occurring within the neonatal period suggests that most of them have some relationship to the circulatory readjustments which normally occur after birth.

He states that particular attention should be called to the ductus arteriosus which in some persons closes with thrombosis of the entire lumen or with formation of a clot on each end of the obstructed vessel. It is obvious that such a thrombus can break off and be carried away into the near-by stream of blood.

In gangrene of the legs a plausible mechanism is the presence of a thrombus in the obliterated umbilical artery, which could extend beyond the defunctionalized segment into the hypogastric or even into the common iliac. In our patient, since there was a large slough of the buttock, and since the femoral artery was never palpable, it must be assumed that the common iliac vessel was thrombosed and that the gluteal vessels were involved in the thrombosis.

PROGNOSIS AND TREATMENT

The prognosis is, of course, dependent upon the severity of the condition, the degree of involvement of the large vessels, and the rapidity of formation of collateral circulation. If the changes are not striking it is difficult to determine accurately whether the condition will go on to eventual gangrene and loss of the limb, or will show a steadily diminishing degree of mottling, cyanosis, and pallor with eventual recovery. The initial management, therefore, will depend a great deal on the surgeon's estimate of whether he is dealing with a beginning gangrene or not.

Conservative, expectant management is in order if eventual recovery without gangrene is expected. Cleansing the entire extremity and dressing it under strict aseptic conditions is of extreme importance in avoiding any secondary infection. No heat should be applied to the affected part and it should be kept at room temperature. General care including body warmth, oxygen, antibiotics, vasodilators, and nutrition are of great importance. In our patient, the extremity was cyanotic, mottled and cold to the touch, and the leg was flaccid. There was no femoral pulsation. Gangrene had not yet supervened. It was considered wise, therefore, to treat it conservatively. This was considerably

complicated by the generally poor condition of the patient. Whether the brain injury was due to anoxia alone or to thrombosis of cerebral vessels is impossible to say. The necessity for amputation of the affected extremity must be kept in mind as an ultimate means of relief in all these patients.

An analysis of the 47 cases in the literature shows the following results. Of 9 patients with involvement of the lungs, kidney, brain, or celiac artery, all died; of the remaining 38 patients, 8 had the affected extremity amputated, of whom 2 died, five recovered, and the end result in one case was not reported. Of the 30 patients who were treated conservatively, 13 died and 17 recovered, many of these following a slough of the gangrenous part or an autoamputation of the extremity.

It is the consensus of opinion that a very conservative position be maintained when dealing with an arterial thrombosis in infancy. By avoiding an amputation in what appears to be a hopeless case, one may succeed in establishing sufficient collateral circulation to obtain a good functioning extremity with a loss of only a very small portion of it. Although our patient at the end of six months had no palpable femoral pulse and did not have satisfactory use of his leg, still he had lost only one toe in the process, and his leg and foot had been saved.

SUMMARY

1. Impending gangrene of the extremity in a newborn infant, probably due to thrombosis of the common iliac artery, is reported.

2. The 47 previously reported cases are analyzed and discussed.

3. Conservative management with strict asepsis to avoid secondary infection is the preferred treatment.

4. Amputation of the extremity should be avoided or deferred as long as possible.

REFERENCES

1. Martini: Mag. f. d. Ges. Heilk. **27**: 428, 1828.
2. Leopold, Ahlfeld, and Weichert: Arch. f. Gynäk. **10**: 189, 1876.
3. Gross, R. E.: Am. J. Dis. Child. **70**: 61, 1945.
4. Heller, G., and Alvari, G.: Am. J. Dis. Child. **62**: 133, 1941.
5. Dohan, F. C.: J. PEDIAT. **5**: 756, 1934.

Medical Progress

SOME RECENT ADVANCES IN POLIOMYELITIS

ROBERT WARD, M.D.
NEW YORK, N. Y.

DIFFERENT IMMUNOLOGIC TYPES OF POLIOMELITIS VIRUS

THE separation of poliomyelitis viruses into different immunologic types has recently been studied systematically by a number of workers.[1a, b, c, 2] At the present writing three different immunologic types have been described. Although it is not known how many more exist, it is suspected on the basis of thirty-nine representative strains already classified, that the number of additional types may not be large. The multiplicity of types has a vital bearing on problems of epidemiology and immunology including that of possible prevention by means of vaccination. In the absence of a simple, specific "glassware" serologic test for poliomyelitis, the differentiation of types has been approached by three experimental methods: (1) second attack rates in paralyzed convalescent monkeys, (2) reciprocal vaccination-immunity, and (3) serum neutralization tests. Agreement in results obtained by these three methods has been reported.[2] The first method depends on the failure, observed some time ago, to reinfect with *homologous* virus monkeys paralyzed and convalescent from a first attack. On the other hand, second attacks are successfully produced in the same animals injected with *heterologous* virus. Among the disadvantages of this method would seem to be: (A) that the second attack rate with heterologous virus is about 50 per cent and always less than the normal control attack rate,[1a] and therefore a large number of monkeys is required to render the results significant, and (B) that the second attack in a convalescent monkey with residual paralysis is sometimes difficult to evaluate.[2] The second method, reciprocal vaccination-immunity, is based on the demonstration of active immunity induced in monkeys following intramuscular injection of active virus. Thus monkeys which are given repeated intramuscular injections of strain A will resist intracerebral challenge with strain A but will respond in all-or-none fashion to subsequent challenge with strain B depending on whether or not strain B belongs to the same type as strain A. The third method is the serum neutralization test which is carried out by adding virus to serum of vaccinated-immune monkeys and then inoculating the mixture intracerebrally into monkeys.[2, 3] Immune serum will neutralize homologous virus, e.g., monkeys will not be paralyzed. Contrariwise, the same immune serum mixed with heterologous virus will not protect monkeys. Because monkeys must be used in each test all three methods of type differentiation are cumbersome and time-consuming. Nevertheless, it would appear from the work already accomplished, that

From the Department of Pediatrics, New York University-Bellevue Medical Center, New York City.

eventually we should have a clearer understanding of the number and distribution of the various types of poliomyelitis viruses.

Suggestive evidence that the three known types of poliomyelitis virus are widely distributed in this country is derived from the finding of neutralizing antibody against each of the three types in gamma globulin fractions of pooled adult plasma.[4]

ATTEMPTS TO PURIFY POLIOMYELITIS VIRUS

The purification of poliomyelitis virus has long been the goal of a number of investigators. The tasks of unravelling the physical and chemical properties of the virus and the preparation of antigens and vaccines will be facilitated by separating the virus from tissue components. Recently Warren, Weil, Russ, and Jeffries[5] have used protamine sulfate with success in partially purifying a number of viruses including that of poliomyelitis. The addition of protamine sulfate to brain suspensions containing the virus results in the precipitation of much of the extraneous material leaving virtually all of the virus in the supernatant fluid. Another method of purification has been devised by LoGrippo,[6] who found that when suspensions of virus were mixed with a strong base anion exchange resin (Amberlite XE-67), the virus became attached to the resin (probably by adsorption rather than by ion exchange) and could be eluted subsequently with 10 per cent disodium acid phosphate. By this means over 90 per cent of the nitrogenous material was removed (e.g., remained on the resin) while most of the virus was recovered in the eluate. This technique proved to be applicable to suspensions of human stool as well as of mouse central nervous system.

THE COXSACKIE GROUP OF VIRUSES

One of the most important recent discoveries in this field is the detection of a "new" virus, or group of viruses, in the stools of patients diagnosed as having poliomyelitis. Dalldorf and Sickles first described this agent[7a, b] which upon injection gives rise to paralysis and death in baby mice. Dalldorf has suggested the provisional term "Coxsackie group of viruses" after the village in New York state where patients infected with this type of virus were first recognized. Coxsackie, or C virus for convenience, resembles poliomyelitis virus in certain properties but differs sharply from it in certain other properties. Like poliomyelitis virus, C virus is detected in human feces and pharyngeal secretions; it has also been isolated from sewage and flies.[8] On the other hand, C virus differs from poliomyelitis virus in respect to host range, tissue affinities, pathologic lesions, and immunologic characteristics. The C virus is pathogenic for suckling mice and suckling hamsters but not for rhesus monkeys (*Macaca mulatta*), mature mice, or mature hamsters. Melnick and Ledinko[9] described infection in cynomolgus monkeys (*Macaca cynomolgus, Macaca irus*) fed their Ohio strain of C virus; a virus carrier state with fever resulted. The C virus was recovered from the feces and throat swabs, and serum antibodies (both neutralizing and complement fixing) were demonstrated on the twenty-fourth day. Chimpanzees also develop an inapparent carrier state. Histologic exami-

nation of the hindbrain, spinal cord, and leg muscles of the cynomolgus monkeys revealed no lesions. Dalldorf and his associates[7b] were unable to infect newborn guinea pigs, fertile hens' eggs, or monkeys. In the writer's laboratory,[10] newborn rabbits, newborn albino rats, and immature rhesus monkeys proved resistant to a strain (isolated in New York City) which produced typical changes in newborn mice, hamsters, and cotton rats.

The experimental disease in baby rodents is characterized by paralysis of the extremities appearing two to ten days following either intracerebral or intra-abdominal inoculation. Widespread pathologic changes are found in the skeletal muscles. The damage seems to begin as hyaline degeneration of the muscle fibers progressing to extensive necrosis and calcification. There may be an intense cellular infiltration chiefly with mononuclear elements. The sarcolemma cells show active proliferation, and reparative processes are seen early. Focal cellular infiltrations have been seen in the brains of mice paralyzed with some strains but with other strains the central nervous system is apparantly devoid of lesions. We have seen neuronal necrosis and neuronophagia in the spinal cord of a paralyzed mouse in addition to typical muscle lesions.[10] Weller and associates have reported changes in the heart muscle, lungs, liver, adipose tissue, and pancreas of newborn rodents infected with strains from Massachusetts.[11]

There is evidence that C virus exists in multiple serologic types. Sickles and Dalldorf[12] have reported three serologic types, and Melnick, Shaw, and Curnen[8] have demonstrated the existence of at least two others. Howitt reported the detection of C viruses in ninety-eight individuals. She found strains related serologically to Dalldorf's Types I and II and two strains which were not.[15a, b] The number of different types which may exist is unknown at present. It is important to appreciate this in attempting to evaluate the results of diagnostic serologic tests on the sera of patients whose stools failed to yield virus or were not tested. There appears to be no immunologic relationship at present between certain C viruses and strains of poliomyelitis virus (Lansing, Aycock, North Carolina, 1948, and Texas, 1948).[7b, 13] Melnick and associates[14] described the successful isolation of both poliomyelitis virus and C virus from the stools of each of two patients diagnosed as "summer grippe." Both patients developed neutralizing and complement-fixing antibodies to C virus during convalescence. Whether or not these patients also developed neutralizing antibodies to their own strains of poliomyelitis virus was not determined because the infectivity of the strains for monkeys was too low to carry out neutralization tests. Both poliomyelitis and C viruses were detected in the stools of fifteen patients diagnosed as poliomyelitis in Easton, Pa. Melnick found that neutralizing antibody for both viruses developed during convalescence in two patients with paralysis.[28]

Various clinical syndromes have been associated with C virus. In addition to being isolated from patients diagnosed as paralytic and nonparalytic poliomyelitis and "summer grippe," C virus has been detected in patients with a variety of clinical diagnoses, aseptic meningitis, encephalitis, epidemic pleurodynia, influenza, infectious mononucleosis, appendicitis, sinusitis, and "fever of

unknown origin." Most of the reported cases occurred during the warm season. The majority of patients yielding virus were children although tests on a few adults have also been positive. In the cases diagnosed as poliomyelitis or aseptic meningitis the cerebrospinal fluid (CSF) showed a pleocytosis with with predominance of mononuclear elements and slight elevation of protein in some, whereas in those cases described as "fever of unknown origin," "summer grippe" (1 case), and epidemic pleurodynia, the CSF was normal.[15]

Melnick, Shaw, and Curnen[8] have found C virus in sewage and nonbiting filth flies which have also on occasion provided extrahuman sources of poliomyelitis virus. The positive sewage samples were obtained in 1948 from three cities in Connecticut and three cities in North Carolina at times when "mild poliomyelitis" was prevalent in Connecticut, and a severe epidemic of classical poliomyelitis was present in North Carolina. The C virus was found in flies trapped in Connecticut, North Carolina, and Texas. Some of the Texas specimens yielded both C virus and poliomyelitis virus.

What is the relation between C virus and poliomyelitis virus? Is the finding of both agents in the same patient and same batches of flies coincidence or does it indicate some close biologic relationship as yet not understood? In any event, infection with C viruses appears to be widely distributed. Evidence for their activity has been found in many states between New England and Texas, in Alaska, Prince Edward Island, Iceland, and Sweden. The task of unravelling the natural history of C virus infections will doubtless be furthered by systematic virologic and serologic work combined with careful clinical studies on patients diagnosed as having poliomyelitis or suffering from various febrile illnesses of unknown etiology.

A PROTECTIVE SUBSTANCE AGAINST POLIOMYELITIS FOUND IN HUMAN MILK AND THE MILK OF CERTAIN COWS

Sabin reported recently the finding of an antipoliomyelitic substance in human milk.[16] The investigation was carried out to determine whether or not prolonged breast feeding, still practised in certain parts of the world, might be a factor in keeping down the incidence of paralytic poliomyelitis. It was reasoned that because the alimentary tract is a most likely portal of entry of poliomyelitis, the presence of a neutralizing substance in milk takes on added significance. Specimens of milk and serum were taken simultaneously from 30 mothers at various stages after delivery and tested for protective effect against about 50 LD_{50} doses of Lansing poliomyelitis virus. All the sera and the milk of 25 of the 30 mothers contained the neutralizing substance. All 10 milk specimens obtained between two and five days post partum and 15 of the 20 obtained thirty-eight to 340 days post partum showed antipoliomyelitic effect. Sabin observed that most of the milk specimens obtained from three and one-half to eleven months after delivery, at a time when antibody transmitted via the placenta is usually absent, still contained the neutralizing substance. There was no correlation, however, between the concentration of the substance in the serum and in the milk of individual mothers, which suggested that the substance in milk was not antibody. In support of this idea,

Sabin found that 7 of 8 selected milk specimens afforded protection against Japanese B encephalitis virus to which these mothers had not been exposed while serums from the same individuals were negative. It seems, moreover, that different factors were involved in the action against these two viruses because 2 milk specimens, devoid of protection against poliomyelitis virus, were effective against Japanese B virus and the strongest antipoliomyelitic milk failed to protect against Japanese B virus.

Similar tests carried out on the milk obtained separately from nine cows showed antipoliomyelitic effect in only two.

Judgment concerning the possible practical implications of these intriguing observations must await an experiment to determine whether or not oral infection in primates can be prevented or altered by the antipoliomyelitic substance. At this point it is interesting to speculate on the striking age distribution of patients with paralytic poliomyelitis in a recent severe epidemic in Canadian Eskimos.[17a, b] Although the percentage distribution was approximately equal for all ages above 4 years, *there were no paralyzed patients under 3 years.* Inasmuch as a reported common practice among Eskimo mothers is to nurse their offspring for three or more years, a possible connection between the sparing of those under 3 years and Sabin's milk factor seems worth investigating.

THE CHANGING AGE INCIDENCE OF POLIOMYELITIS

A striking phenomenon in the epidemiology of poliomyelitis is the change in the pattern of age selection in certain parts of the world during the last half century. In the American, Scandinavian, and Australian epidemics of twenty to forty years ago between 80 and 90 per cent of the patients were under 5 years of age. Today, on the other hand, perhaps three-fourths of the cases occur in individuals over 5 years, so that in countries afflicted with epidemics* the disease can no longer be called "infantile paralysis."[18-22]

It has been suggested[24] that the apparent variation in age distribution in Massachusetts has been due to changes in the age distribution of the population and to an increase in the reporting of nonparalytic cases. An analysis of the shift in age selection made on the basis of *age-specific rates* should exclude the effects of population changes. By the same token, an analysis of paralytic cases only or of age-specific mortality rates would be valuable since these should not be particularly affected by the increased reporting of nonparalytic poliomyelitis. Sabin[22] has compared age-specific attack rates based on paralytic cases only in several Swedish cities in 1911 and 1913 with those in 1935-37. In the later epidemic not only was a smaller proportion attacked under 4 years of age, but the risk of getting paralyzed was as great at the age 15 to 24 years as at 0 to 4 years, while at the age 5 to 14 years it was greatest of all.

Pichel[19] has made a critical analysis of the changing age incidence of poliomyelitis in Connecticut between 1921 and 1947. On the basis of age-specific attack rates the results for the group aged 0 to 4 years showed a downward trend

*In certain nonepidemic areas the shift in age selection has apparently not taken place, the bulk of the cases still occurring in those below the age of 5 years.[23]

while the percentage distribution of cases rose for the groups aged 5 to 9 and 10 to 14 years. The percentage distribution of age-specific mortality rates showed similar trends for the age groups mentioned.

These findings suggest that poliomyelitis in certain areas has actually become less "infantile" now than formerly, and that the changes cannot be entirely explained by the aging of the population nor by the increased reporting of nonparalytic cases. The same type of change has not occurred in the age distribution of measles, whooping cough, and diphtheria. Although there is no explanation at present for the phenomenon it should be studied vigorously because it seems quite likely to have an important bearing on the natural history of poliomyelitis.

THE RELATION OF PHYSICAL ACTIVITY TO THE COURSE OF THE DISEASE

It is only too apparent that little can be done at present to prevent poliomyelitis. There is no serum, vaccine, or chemoprophylactic agent of proved value to man. On the other hand, we can postpone to another season such elective operations in the oropharynx and nasopharynx as the removal of tonsils and adenoids. It is usually possible, moreover, for individuals in a noninfected community to forego visiting an epidemic area. Another preventive measure, suspected from casual clinical observation, and from experiments in monkeys, has recently been analyzed and its application to man established. During the English epidemic of 1947 Russell[25a, b, c] questioned 89 convalescent patients old enough to give an accurate history and found that 80 per cent of those who developed slight or no paralysis either went to bed at the onset of the preparalytic phase or admitted very slight activity for less than twenty-four hours before going to bed; the corresponding figure for those with severe paralysis was only 8 per cent. On the other hand, in those persisting with physical activity for more than twenty-four hours 62 per cent suffered severe paralysis and in only 8 per cent was the paralysis slight. Hargreaves[26] confirmed these observations in the same outbreak. In this country Horstmann[27] studied 411 patients from three epidemics in respect to the amount of physical activity carried out around the time of onset of their disease. She found that when physical activity was continued after the second phase or *major illness* it was associated with a significant increase in the incidence and severity of subsequent paralysis. By the same token, a greater porportion of nonparalytic than paralytic patients gave a history of bed rest or minimal activity after the onset of the major illness. On the other hand, analysis revealed no correlation between physical activity performed at the time of the first phase (minor illness) or prior to the onset of the major illness and the development or severity of paralysis.

Little is known about the factors responsible for this apparent relation between exercise and subsequent paralysis. There is evidence that virus may invade the central nervous system some time before the appearance of paralysis, and the possibility exists that muscular work may in some way alter the metabolism of the nerve cell making it more vulnerable to the virus. At all events the

story seems clear enough to warrant careful observation of individuals during the poliomyelitis season and the prompt confinement to bed of those with incipient signs of the disease.

REFERENCES

1. a. Bodian, D.: Differentiation of Types of Poliomyelitis Viruses. I. Reinjection Experiments in Monkeys (Second Attacks), Am. J. Hyg. **49**: 200, 1949.
   b. Morgan, I. M.: II. By Reciprocal Vaccination-Immunity Experiments, Am. J. Hyg. **49**: 225, 1949.
   c. Bodian, D., Morgan, I. M., and Howe, H. A.: III. The Grouping of Fourteen Strains into Three Basic Immunological Types, Am. J. Hyg. **49**: 234, 1949.
2. Kessel, J. F., and Pait, C. F.: Immunologic Groups of Poliomyelitis Viruses, Am. J. Hyg. **51**: 76, 1950.
3. Brown, G. C., Francis, T., Jr., and Ainslie, J. D.: Immunologic Relations and Comparative Invasiveness of Strains of Poliomyelitis From Recent Epidemics, Federation Proc. **8**: 401, 1949.
4. Bodian, D.: Neutralization of Three Immunological Types of Poliomyelitis Virus by Human Gamma Globulin, Proc. Soc. Exper. Biol. & Med. **72**: 259, 1949.
5. Warren, J., Weil, M. L., Russ, S. B., and Jeffries, H.: Purification of Certain Viruses by Use of Protamine Sulfate, Proc. Soc. Exper. Biol. & Med. **72**: 662, 1949.
6. LoGrippo, G. A.: Partial Purification of Viruses With an Anion Exchange Resin, Proc. Soc. Exper. Biol. & Med. **74**: 208, 1950.
7. a. Dalldorf, G., and Sickles, G. M.: An Unidentified, Filtrable Agent Isolated From the Feces of Children With Paralysis, Science **108**: 61, 1948.
   b. Dalldorf, G., Sickles, G. M., Plager, H., and Gifford, R.: A Virus Recovered From the Feces of "Poliomyelitis" Patients Pathogenic For Suckling Mice, J. Exper. Med. **89**: 567, 1949.
8. Melnick, J. L., Shaw, E. W., and Curnen, E. C.: A Virus Isolated From Patients Diagnosed as Nonparalytic Poliomyelitis or Aseptic Meningitis, Proc. Soc. Exper. Biol. & Med. **71**: 344, 1949.
9. Melnick, J. L., and Ledinko, N.: Injection of Cynomolgus Monkeys With the Ohio Type of Coxsackie Virus (C Virus), J. Immunol. **64**: 101, 1950.
10. Ward, R., and Rader, D. L.: (Unpublished observations.)
11. Weller, T. H., Enders, J. F., Pappenheimer, A. M., Buckingham, M., and Finn, J. J.: Isolation of a Filtrable Agent From Throat Washings Collected During an Outbreak of Epidemic Pleurodynia. Paper Read at the Meeting of The Society for Pediatric Research on May 8, 1950, at French Lick, Ind.
12. Sickles, G. M., and Dalldorf, G.: Serologic Differences Among Strains of the Coxsackie Group of Viruses, Proc. Soc. Exper. Biol. & Med. **72**: 30, 1949.
13. Curnen, E. C., Shaw, E. W., and Melnick, J. L.: Disease Resembling Nonparalytic Poliomyelitis Associated With a Virus Pathogenic For Infant Mice, J. A. M. A. **141**: 894, 1949.
14. Melnick, J. L., Ledinko, N., Kaplan, A. S., and Kraft, L. M.: Ohio Strains of a Virus Pathogenic For Infant Mice (Coxsackie Group). Simultaneous Occurrence With Poliomyelitis Virus in Patients With "Summer Grippe," J. Exper. Med. **91**: 185, 1950.
15. a. Howitt, B. F., and Benefield, U. R.: Use of Complement Fixation in the Differentiation of Strains of Coxsackie Virus, Proc. Soc. Exper. Biol. & Med. **73**: 90, 1950.
   b. Howitt, B. F.: Paper Presented at the Symposium on Coxsackie Viruses Held at the Meeting of the American Association of Immunologists, Atlantic City, N. J., April 18-21, 1950.
16. Sabin, Albert B.: Antipoliomyelitic Substance in the Milk of Human Beings and Certain Cows, Presented at the meeting of the American Pediatric Society, May 9-10, 1950, French Lick, Ind.
17. a. Peart, A. F. W.: An Outbreak of Poliomyelitis in Canadian Eskimos in Wintertime, Epidemiological Features, Canad. J. Pub. Health **40**: 405, 1949.
   b. Rhodes, A. J., Clark, E. M., Goodfellow, A., and Donohue, W. L.: An Outbreak of Poliomyelitis in Canadian Eskimos in Wintertime, Laboratory Features, Canad. J. Pub. Health **40**: 418, 1949.
18. Burnet, F. M.: The Epidemiology of Poliomyelitis, With Special Reference to the Victorian Epidemic of 1937-38, Med. J. Australia **1**: 325, 1940.
19. Pichel, J. I.: The Age Incidence of Poliomyelitis in Connecticut 1921-1947, Yale J. Biol. & Med. **22**: 327, 1950.
20. Dauer, C. C.: Trends in Age Distribution of Poliomyelitis in the United States, Am. J. Hyg. **48**: 133, 1948.

21. Gilliam, A. G.: Changes in Age Selection of Fatal Poliomyelitis, Pub. Health Rep. 63: 677, 1948.
22. Sabin, A. B.: Epidemiologic Patterns of Poliomyelitis in Different Parts of the World. In: Poliomyelitis, Papers and Discussions Presented at the First International Poliomyelitis Conference, Philadelphia, 1949, J. B. Lippincott Company, p. 3.
23. Paul, J. R.: Poliomyelitis in Japan, Am. J. Hyg. 45: 206, 1947.
24. Horton, R. J. M., and Rubenstein, A. D.: The Age Distribution of Poliomyelitis in Massachusetts, New England J. Med. 239: 169, 1948.
25. a. Russell, W. R.: Poliomyelitis: The Preparalytic Stage, and the Effect of Physical Activity on the Severity of Paralysis, Brit. M. J. 2: 1023, 1947.
b. Russell, W. R.: International Poliomyelitis Congress. In: Poliomyelitis, Papers and Discussions Presented at the First International Poliomyelitis Conference, Philadelphia, 1949, J. B. Lippincott Company, p. 104.
c. Russell, W. R.: Paralytic Poliomyelitis: The Early Symptoms and the Effect of Physical Activity on the Course of the Disease, Brit. M. J. 1: 465, 1949.
26. Hargreaves, E. R.: Poliomyelitis: Effect of Exertion During Preparalytic Stage, Brit. M. J. 2: 1021, 1948.
27. Horstmann, D. M.: Acute Poliomyelitis: Relation of Physical Activity at the Time of Onset to the Course of the Disease, J. A. M. A. 142: 236, 1950.
28. Melnick, J. L.: Personal communication.

Psychologic Aspects of Pediatrics

FEEBLE-MINDEDNESS AND PSEUDOFEEBLE-MINDEDNESS

HARRY BAKWIN, M.D.
NEW YORK, N. Y.

THE term feeble-mindedness is broad and includes a large number of widely different conditions, related only by the fact that mental power is reduced to a level which is compatible at best with a low order of performance. Lewis[1] has divided the feeble-minded into two groups. The first and by far the larger consists of individuals whose deviation is physiologic and quantitative rather than pathologic and qualitative. They represent the lower part of the normal distribution curve of intelligence. If we use an analogy with body height, they are the persons who are conspicuous by their shortness, yet they are not abnormal.

The second group is made up of individuals who are definitely abnormal. In them the mental defect is associated with other pathologic conditions, e.g., amaurotic family idiocy, kernicterus. Continuing the analogy to height, individuals in this group correspond to the achondroplastic or pituitary dwarf. They are in no sense mere variations on a normal distribution curve.

SIMPLE FEEBLE-MINDEDNESS

In the first group mental capacity is limited by the genetic endowment. In a sense the deficiency here, since it is determined by the germ plasm, may be looked upon as hereditary. Yet it should be kept clearly in mind that this is not necessarily so. Sex which is also a germ plasm factor is not generally regarded as hereditary. The intelligence of children is positively correlated with that of the parents (r equals .49)[2] and most feeble-minded children come from parents whose intelligence is in the low range; but there is considerable variability and parents of high intelligence may and often do give birth to a feeble-minded child; and, on the other hand, feeble-minded parents may have a child of superior intelligence.

Children in this group usually come from low income families in contrast to those in the second group who are distributed uniformly among all socio-economic strata. In the large majority of instances the degree of mental deficiency is mild and intelligence quotients of 50 to 70 predominate. The children present no unusual physical features. As adults they are well suited to perform the many simple tasks necessary in society.

The diagnosis is made on the slowness in motor and speech development, the child's general behavior, the poor performance at school, and the results of intelligence testing.

From the Department of Pediatrics, College of Medicine, New York University-Bellevue Medical Center.

MENTAL DEFICIENCY ASSOCIATED WITH DISEASE

The second and much smaller group includes individuals in whom mental deficiency is associated with a large number of etiologically and anatomically unrelated pathologic conditions. In some, feeble-mindedness is a constant and prominent feature, for example mongolism, amaurotic family idiocy; in others it may or may not be present, e.g., gargoylism, tuberous sclerosis, and premature cranial synostosis. In some instances the defect is implicit in the germ plasm, e.g., amaurotic family idiocy, phenylpyruvic oligophrenia, familial microcephalic idiocy; in others it is acquired, e.g., mental deficiency due to maternal infection with rubella or lead encephalopathy. An important feature of this group is that it contains, among others, some individuals who started life with a normal intellectual endowment.

The extent of the mental defect depends largely on the etiology. Children whose disease stems from a germ plasm defect or whose injury took place be-

TABLE I. MENTAL DEFICIENCY ASSOCIATED WITH ORGANIC DISEASE

A. GERM PLASM DEFECTS
Cerebroretinal degenerations: amaurotic family idiocy and others
Niemann-Pick disease
Galactosemia
Phenylpyruvic oligophrenia
Pseudohypoparathyroidism; the mental defect is usually mild
Muscle dystrophy
Familial oligoencephaly (Benda)
Nevoid amentia (Parkes Weber-Dimitri disease)
Familial microcephalic idiocy
Macrocephalic idiocy
Tuberous sclerosis
Lawrence-Moon-Biedl syndrome
Degenerative diseases affecting chiefly the white matter: encephalitis periaxialis diffusa of Schilder, Pelizaeus-Merzbacher disease
Heller's disease (This may be schizophrenia)
Hydrocephalus; may be acquired postnatally
Anencephalus
Gargoylism
Friedreich's ataxia
Congenital atonic diplegia
Ocular hypertelorism
Premature cranial synostosis
Cleidocranial dysostosis
B. ENVIRONMENTAL
1. Prenatal
Maternal infections: rubella, toxoplasmosis
X-ray irradiation of mother during pregnancy
Anoxic disease of mother during pregnancy
Mongolism
Cretinism
Pituitary hypogenitalism
2. Natal and Postnatal
Isoimmunization, kernicterus
Laceration of brain at or after birth
Anoxic damage to brain at or after birth
Subdural hematoma
Infections: encephalitis, meningitis
Pertussis
Lead poisoning
Hypothyroidism
Hypoglycemia
Recurrent convulsions (?)

tween conception and birth are usually severely, often totally, defective. In some of these conditions, however, the mental weakness may be mild, e.g., tuberous sclerosis.

Children in whom damage to the brain took place at or after birth show a widely variable picture, depending on the time and character of the injurious agent. Injury as a result of Rh incompatibility leads to severe retardation (kernicterus). Encephalitis during the first two years of life usually causes serious mental retardation; thereafter, the disturbances, if any, are principally neurologic and emotional. Anoxic damage to the brain at or after birth may be associated with any degree of retardation or none at all. The various causes of mental deficiency associated with disease are listed in Table I.

PSEUDOFEEBLE-MINDEDNESS

There is a growing appreciation that a sizable group of children who are labelled as feeble-minded actually have mental capabilities which are well within the normal range.[3] Various terms have been applied to this group: pseudo-feeble-mindedness, apparent feeble-mindedness, nongenuine feeble-mindedness, pseudodeterioration.

The reasons why children are falsely regarded as feeble-minded are listed in Table II.

TABLE II. THE ETIOLOGY OF PSEUDOFEEBLE-MINDEDNESS. CONDITIONS FOR WHICH CHILDREN ARE SOMETIMES FALSELY LABELLED AS FEEBLEMINDED

1. Special language disability, i.e., reading, spelling
2. Delayed speech development
3. Severe early illness with delay but not prevention of mental development
4. Brain injury with interference of some but not all mental qualities
5. Physical handicaps: vision, hearing, motor (e.g., athetosis)
6. Lack of social opportunities or stimulating environment
7. Schizophrenia
8. Hydrocephalus
9. Epilepsy
10. Drug therapy in epilepsy
11. Hypothyroidism
12. Improper testing
    - Inexperienced tester
    - Emotional blocking—uncooperativeness
      restlessness
      fear
    - Fatigue

A further reason for mistakenly branding a child as feeble-minded is a failure to appreciate the ability of intact areas of the brain to take over functions ordinarily carried out by ones which happen to be traumatized.

Developmental History.—In general, delay in motor and speech development is a good indication of feeble-mindedness. However, in a child with cerebral damage, whether due to anoxia at birth or hydrocephalus or other cause, motor development may be postponed considerably and yet the mental capacity may remain within the average range or even be superior. A delay in starting to talk, even as late as 3 years of age, is not a great rarity and is generally associated with alterations in lateral dominance. Defective hearing is another cause. Parental overprotection may contribute to the delay. In young children with

schizophrenia mutism is a frequent symptom. Both motor and speech retardation are often seen in children reared in the unstimulating atmosphere of an institution.

The response to toilet training is not a good criterion of feeble-mindedness. Unless severely retarded, feeble-minded children respond to toilet training at about the same age as children with normal or superior mentality. Difficulties with bladder training are encountered in children with the enuretic make-up regardless of mental status.

Defects in vision and hearing may confuse. The visual defect may be in fusing images and may not be apparent in the usual tests for vision. Under these circumstances images are seen above one another or alongside one another. The images received by the two eyes may also be of different sizes (aniseikonia).

A hearing defect may be gross or it may be restricted to a limited area of the hearing spectrum (regional deafness) and so be missed in the usual examination. A child may have an auditory impairment which interferes seriously with language development, yet he can distinguish the sounds of the 256 or 512 d.v. tuning forks and can respond to the low frequency whispers, clicks, and clapping of the hands that are commonly employed to test hearing.[4] Such a child, with some hearing but not enough, is often slow to talk, his utterances are garbled and distorted, he often ignores commands and does not answer when spoken to, he is bored at home and inattentive at school, he does not play with other children, and he may present serious emotional disturbances such as shyness and reticence or noisy aggressiveness. Hearing is closely related to the development of language on which depends, in turn, a considerable amount of general behavior. Only later in childhood does reading become a medium of communication. The deaf child is frequently regarded as mentally retarded.

Postnatal Damage to the Brain.—The most common cause of this condition is anoxic injury at or shortly after birth. All degrees of disturbance may result from behavior disturbances without any direct interference in mental functioning to complete idiocy. A diagnosis of mental retardation should not be made unless the deficiency is severe.

There are three reasons for postponing judgment in doubtful cases: (1) good mental functioning may be obscured by the motor and other defects; (2) injured cells in the brain may recover and become functional; and (3) reorganization of cerebral function may take place with restitution of function.

The brain of the human being, as well as of other mammals, shows remarkable recuperative powers following injury. The restitution of function may take place by reorganizing and adapting mental faculties which are relatively intact.[5] In a sense the patient by-passes his defect by making use of his past experiences and his reasoning powers. It follows that adults who have accumulated experience and who have already developed their reasoning powers at the time of the injury will adapt in this way more readily than young children in whom the acquisition of these adaptive devices is hampered by the presence of a cerebral injury.

It is important to remember, however, that function may be recovered in children. Children tolerate destruction of larger masses of brain tissue than

do adults.[6] Moreover localization of function in them has not progressed as in adults, and consequently, other areas mediate the lost functions more effectively.

The nature of the functional deficit following cerebral injury depends on: (1) the amount of destroyed tissue, the greater the mass, the greater the deficit; (2) on the age at which the injury takes place, the child showing greater plasticity than the adult; (3) on whether the injury was simple or repeated, the individual apparently tolerating repeated small injuries over a prolonged period of time (as in seniles) better than a single large injury; and (4) on the localization of the damage.

Restitution of function is generally not complete. The presence of defects may not be readily apparent but they can usually be elicited by suitable methods. Thus the child with cerebral damage may be able to describe accurately the details of a picture if he is given sufficient time. But if the picture is flashed before him, or is shown in poor light or is obscured in other ways, he will not be able to respond as well as does the normal child.

The factors which may interfere with mental performance in the child with damage to the brain are the following:

1. Injury to the cerebral cortex. Involvement of the cortical areas which are concerned with mental functioning.

2. General motor disability interfering with motor development and with achievement on performance tests.

3. Motor disability affecting the muscles of speech, thereby slowing down verbal expression and making it difficulty intelligible and fatiguing.

4. Defects in vision and hearing.

5. Defects in the use of language owing to (a) injuries to the cortical areas which govern the language functions, (b) alterations in lateral dominance made necessary by the particular type of motor involvement with corresponding failure to establish clear-cut cerebral dominance, (c) difficulties in articulation, and (d) life in an unstimulating environment.

6. Emotional factors. The disturbed emotional state of many children with cerebral palsy is due to (a) involvement of the extrapyramidal system which has to do with emotional reactivity, (b) the reaction of persons in the environment to the child's deficiencies, and (c) the child's own reaction to his shortcomings.

7. Inadequate opportunities for social living.

8. Repeated convulsions and the use of antiepileptic drugs in children with convulsions.

Children with athetosis, excepting the cases resulting from Rh incompatibility, usually have normal mentality.

The convulsions which are frequently present in children with cerebral damage may or may not be directly related to the injury. In many the convulsions are associated with the epileptic constitution and are set off by the injury to the brain.

Many children with hydrocephalus, even when well-marked, have normal or even superior intelligence. Their reactions are slow and deliberate but their intellectual performance may be surprisingly good.

Childhood schizophrenia may be readily confused with feeble-mindedness. The differential diagnosis is made on the basis of a history of normal development and then regression, as well as on the presence of other symptoms and signs of schizophrenia.

Unstimulating Environment.—This may be a most important consideration. The validity of the results of I. Q. testing implies a certain uniformity of environment. It is apparent that a school age child who has had no education will score low regardless of his innate mental endowment. In estimating intelligence, therefore, the environment must be given due weight. Children may live in an unstimulating environment for many reasons: the home may be inadequate; the child may be living in an institution; he may have a serious visual or auditory defect which interferes with learning; he may have a motor defect which not only prevents normal school attendance but interferes with acquisition of information through the medium of the written word.

Instances of severe retardation on this basis have been referred to by Tredgold[7] as "isolation amentia." Famous examples are Kasper Hauser and the wolf-children described by Gesell.[8] In recent years the most striking examples have been observed in children reared in the unstimulating atmosphere of an institution.[9]

Emotional blocking may seriously interfere with mental performance. The marked improvement in intellectual performance of children following entrance to nursery school[10] has been attributed, in good part, to the effect of personality improvement on mental functioning.[11]

Specific reading and spelling disability may and often do lead to an erroneous diagnosis of feeble-mindedness. Reading disability should be suspected whenever a seemingly intelligent child has difficulty at school.

Epilepsy.—According to Lennox[12] 14 per cent of epileptic patients are definitely deteriorated and another 22 per cent are slightly subnormal (Table III). In some instances the mental defect is only incidentally related to the epilepsy. Here the defect may be looked upon as genetically determined. This accounts for about 30 per cent of the epileptic defectives. In others a traumatic factor, such as injury or a disease, may lead to both mental deficiency and epilepsy. Lennox ascribes 25 per cent of the mental defectives to this group. Deterioration may also result from the repeated anoxia and increased intracranial pressure that accompany recurrent convulsions. Cerebral dysrhythmia, the periods of "shifting dullness," the periods of amnesia, or the manic episodes of a psychomotor seizure may be factors here, too. Lennox places 20 per cent of the defectives in this group.

TABLE III. THE MENTAL STATUS IN EPILEPSY (LENNOX)

	PER CENT	PER CENT
Normal mentality		64
Slightly subnormal		22
Feeble-minded		14
Genetically determined	30	
Traumatic	25	
Resulting from the epilepsy	20	
Pseudodeterioration	25	

In about 25 per cent of the mentally slow epilepties, the alteration in mental functioning is referred to by Lennox as pseudodeterioration. Isolation from normal and stimulating contacts, fear, shame, and discouragement may lead to stagnation of thought and action that closely resembles deterioration. In this group may also be included patients who receive overdosage of sedative drugs. Pseudodeterioration is reversible with proper care.

It is the opinion of Lennox that, excluding brain-injured persons, the I. Q. is unaffected in epilepsy. Among 300 private patients without evidence of cerebral damage, the average I. Q. of children (Stanford-Binet) was 106 and of adults (Wechsler-Bellevue) 113. The variation about the mean was also normal. A study of 28 pairs of monozygotic twins, in which only one of each pair had chronic epilepsy, gave similar evidence. When there was no cerebral pathology, the spread between the two twins was only 4 I. Q. points whereas the spread was 36 points when the brain had suffered gross injury.

Hypothyroidism.—Whereas cretinism is readily recognizable hypothyroidism often presents diagnostic difficulties, especially in its early stages. The clinical features may not be striking and abnormalities in the ossification of the bony centers may be absent. Single determinations of the blood cholesterol are of little value, as are estimations of the basal metabolic rate. Therefore any slow child in whom there is even a vague suspicion of hypothyroidism should have a trial of thyroid medication.

Intelligence Testing.—In general the results of intelligence testing are accurate within 5 points. Gross errors may occur, however, under the following circumstances:

1. The tester is not sufficiently experienced.
2. The child is uncooperative, fatigued, fearful, or restless.
3. The child has a visual or auditory defect.
4. The child has a motor disability which slows down and distorts performance.
5. The child has a specific language disability, e.g., reading, spelling.
6. The child has cerebral damage without overt physical signs but nevertheless is unable to perceive and reproduce certain forms normally.[13]
7. The child has schizophrenia.
8. The child has had frequent convulsions.
9. The child is taking anticonvulsive drugs in amounts sufficient to interfere with mental functioning.
10. The child comes from an unstimulating environment.

TREATMENT

Within recent years a new hopefulness has developed in the attitude toward the feeble-minded child. This is based on an appreciation that improvement may take place, in some instances, spontaneously or with the aid of corrective therapy (the pseudofeeble-minded), and also on the introduction of a number of new therapeutic procedures.

Whatever specific treatment is used it should be combined with proper training for recreation and job placement; drilling in habits of cleanliness, neatness, and courtesy; prevention of emotional disturbances through parental education; correction of defects such as awkward gait, speech impurities, and

dental malocclusion; emphasis on development of character traits such as honesty, loyalty, kindness, and so on.

Reports on the results of treatment with the various new approaches are conflicting. The inconsistencies may well be due, in part at least, to failure to establish clear-cut diagnoses beforehand. It is as though the effect of chemotherapy with the sulfonamides were being tested in the various types of pneumonia without first distinguishing between the possible etiologic agents.

A diagnosis of feeble-mindedness should be made with great caution when a neurologic defect is present. Attention should be given to the motor defect, language training, visual and auditory defects, and emotional factors. In children with hemiplegia, encouraging the use of the noninjured arm, as suggested by Phelps,[14] may aid in developing dominance in uninjured or less injured parts of the brain.

Glutamic acid was introduced to enhance mental power by Price, Waelsch, and Putnam in 1943.[15] Its use for this purpose was discovered accidentally in the course of therapeutic trials with the substance in patients with petit mal and psychomotor attacks. Marked improvement in mental functioning have been reported by some workers,[16] little or none by others.[17]

In a recent study Zimmerman and Burgemeister[16c] have attempted to evaluate the results of glutamic acid therapy in children according to (1) the presence or absence of organic factors, and (2) the presence or absence of associated behavior disturbances. Their report concerns children of I. Q. from 55 to 79. The diagnosis of organically determined retardation was made on the basis of the Rorschach examination which is not generally considered a good criterion of cerebral damage. They obtained the best results in the children without damage of the brain and without associated behavior disturbances. About one-third of the twenty-nine children in this category showed improvement averaging 9.4 I. Q. points. By contrast only about one-fifth of the children with cerebral damage and poor behavior showed improvement, the average rise in I. Q. being only 5.6 points.

Quinn and Durling[17d] were unable to observe any striking change in mental defectives of various clinical types following treatment with glutamic acid. The average improvement amounted to less than 4 I. Q. points. In some children the change was as much as 10 I. Q. points. Most of the improvement took place in the first six months. They concluded that glutamic acid stimulates physical and mental activity in some children.

Benzedrine is of no value in the treatment of mental deficiency.

Recently *an operative procedure*, designed to increase blood flow to the brain (anastomosis of the internal carotid artery and internal jugular vein, with ligation of the proximal end of the jugular vein), has been reported as benefiting about one-third of defective children.[18]

Fluid Restriction.—For a number of years Fay[19] has advocated restriction of fluid intake in children with epilepsy and following trauma. It is his view, based on extensive clinical observation, that many of the symptoms encountered in patients with cerebral damage, i.e., headache, poor ability to concentrate,

distractibility, and headache, can be relieved by reducing intracranial pressure and that this measure will aid recovery of the maximal amount of cerebral activity.

Convulsive Therapy.—The results of convulsive therapy in feeble-minded children as used by Dr. Edwardo Vasco in Colombia have been described by Landis and McCune.[20] Convulsions were induced by Picrotoxin and by electric shock. Mental retests after four months of treatment, and again four months later, showed gains in I. Q. up to 42 points. The cases were not completely studied and it is possible that some of the patients had schizophrenia. It is also possible that some of the initial low I. Q.'s were due to inadequate social stimulation and others to emotional blocking. Nevertheless the shock treatment did seem to induce some sort of improvement. Landis and McCune urge that the method be given a trial in institutions where facilities for careful study are available.

Subdural Hematoma.—The operative procedure developed by Ingraham[21] marks a real advance in the treatment of this condition. By this means a certain number of cases of feeble-mindedness is prevented.

Premature Cranial Synostosis.—Operations designed to permit brain growth by making linear incisions through the skull were performed many years ago in children with familial microcephalic idiocy without success. More recently the operation has been reintroduced for children with premature cranial synostosis by Faber and Towne[22] and successful results have been obtained.

REFERENCES

1. Lewis, E. O.: Types of Mental Deficiency and Their Social Significance, J. Ment. Sc. 79: 298, 1933.
2. Conrad, H. S., and Jones, H. E.: A Second Study of Familial Resemblance in Intelligence: Environmental and Genetic Implications of Parent-Child and Sibling Correlations in the Total Sample, Yearbook Nat. Soc. Stud. Ed. 39 (II): 97, 1940.
3. a. Arthur, G.: Pseudofeeblemindedness, Am. J. Ment. Deficiency 52: 137, 1947.
   b. Doll, E. A.: Is Mental Deficiency Curable? Am. J. Ment. Deficiency 51: 420, 1947.
   c. Kanner, L.: Feeblemindedness: Absolute, Relative, and Apparent, Nerv. Child. 7: 365, 1948.
4. Hardy, W. G.: The Relations Between Impaired Hearing and Pseudofeeble-mindedness, Nerv. Child 7: 432, 1948.
5. Goldstein, K.: The Modifications of Behavior Consequent to Cerebral Lesions, Psychiatric Quart. 10: 586, 1936.
6. Kennard, M.: Cortical Reorganization of Motor Function: Studies on Series of Monkeys of Various Ages From Infancy to Maturity, Arch. Neurol. & Psychiat. 48: 227, 1942.
7. Tredgold, A. F.: Mental Deficiency, ed. 7, Baltimore, 1947, Williams and Wilkins Company.
8. Gesell, A. L.: Wolf Child and Human Child, New York, 1941, Harper & Brothers.
9. a. Durfee, H., and Wolf, K.: Anstaltspflege und Entwicklung im ersten Lebensjahr, Ztschr. f. Kinderforsch. 42: 273, 1933.
   b. Spitz, R. A.: Hospitalism, an Inquiry Into the Genesis of Psychiatric Conditions in Early Childhood, The Psychoanalytic Study of the Child, A Year Book, New York, 1945, International Press.
   c. Goldfarb, W.: Effects of Psychological Deprivation in Infancy and Subsequent Stimulation, Am. J. Psychiat. 102: 18, 1945.
10. Stoddard, G. D., et al.: Intelligence: Its Nature and Nurture, Part I. Comparative and Critical Exposition, Part II. Original Studies and Experiments, Yearbook Nat. Soc. Stud. Ed., new series No. 39, Parts I and II, 1940.
11. Jones, H. E.: Environmental Influences on Mental Development in Carmichael, L., ed.: Manual of Child Psychology, New York, 1946, John Wiley & Sons, Inc., p. 621.
12. Lennox, W. G.: Psychiatry, Psychology, and Seizures, Am. J. Orthopsychiat. 19: 432, 1949.

13. Strauss, A. A., and Lehtinen, L. F.: Psychopathology and Education of the Brain-Injured Child, New York, 1947, Grune and Stratton, Inc.
14. Phelps, W. M.: Paralytic Disorders, Cerebral Palsy, in Nelson's New Loose-Leaf Surgery Vol. 3, New York, 1947, Thos. Nelson & Sons, pp. 1800-1808.
15. Price, J. C., Waelsch, H., and Putnam, T. J.: dl-Glutamic Acid Hydrochloride in the Treatment of Petit Mal and Psychomotor Seizures, J. A. M. A. **122**: 1153, 1943.
16. a. Zimmerman, F. T., and Ross, S.: Effect of Glutamic Acid and Other Amino Acids on Maze Learning in the White Rat, Arch. Neurol. & Psychiat. **51**: 446, 1944.
    b. Zimmerman, F. T., Burgemeister, B. B., and Putnam, T. J.: A Group Study of the Effect of Glutamic Acid Upon Mental Functioning in Children and Adolescents, Psychosomatic Med. **9**: 175, 1947.
    c. Zimmerman, F. T., and Burgemeister, B. B.: The Effect of Glutamic Acid on Border-Line and High Grade Defective Intelligence, New York State J. Med. **50**: 693, 1950.
17. a. Marx, M.: Effects of Supranormal Glutamic Acid on Maze Learning, J. Comp. & Physiol. Psychol. **41**: 82, 1948.
    b. Hamilton, H. C., and Maher, E. B.: Effects of Glutamic Acid on Behavior of the White Rat, J. Comp. & Physiol. Psychol., **40**: 463, 1947.
    c. Stellar, E., and McElroy, W. D.: Does Glutamic Acid Have Any Effect on Learning? Science **108**: 281, 1948.
    d. Quinn, K. V., and Durling, D.: Twelve Months' Study of Glutamic Acid Therapy in Different Clinical Types in an Institution for the Mentally Deficient, Am. J. Ment. Deficiency **54**: 321, 1950.
    e. Kerr, W. J., and Szurek, S. A.: Effect of Glutamic Acid on Mental Function, Pediatrics **5**: 645, 1950.
18. Beck, C. S., McKhann, C. F., and Belnap, W. D.: Revascularization of the Brain Through Establishment of a Cervical Arteriovenous Fistula, J. PEDIAT. **35**: 317, 1949.
19. Fay, T., and Doll, E. M.: Organic Impairment Simulating Mental Deficiency, Am. J. Orthopsychiat **19**: 112, 1949.
20. Landis, C., and McCune, D. J.: The Amelioration of Amentia, Am. J. Ment. Deficiency **54**: 473, 1950.
21. Ingraham, F. D., and Matson, D. D.: Subdural Hematoma in Infancy, J. PEDIAT. **24**: 1, 1944.
22. Faber, H. K., and Towne, E. B.: Early Operations in Premature Cranial Synostosis for the Prevention of Blindness and Other Sequelae, Am. J. M. Sc. **173**: 701, 1927; J. PEDIAT. **22**: 286, 1943.

Comments on Current Literature

PAROTID TUMORS OF CHILDREN

ALTHOUGH neoplastic involvement of the parotid gland in children is comparatively rare, the accurate diagnosis and treatment of parotid tumefaction are important. In the March, 1950, issue of *Surgery, Gynecology and Obstetrics*, John M. Howard, M.D., Arnold J. Rawson, M.D., C. Everett Koop, M.D., Robert C. Horn, M.D., and Henry P. Royster, M.D., F.A.C.S., Philadelphia, Pa.,[1] present an excellent review entitled "Parotid Tumors in Children."

The authors survey the literature since 1920 and include in their summary only those tumors initially observed in patients younger than 16 years of age. In addition, they report twenty-one cases of their own; all of their patients were seen since 1928 on the surgical services of the Hospital of the University of Pennsylvania and of the Children's Hospital of Philadelphia. In all but one instance the clinical impression was verified by histologic study. Seventeen of the twenty-one cases were true neoplasms, fifteen of them primary in the parotid. There were two examples of chronic parotitis, and in one patient the tumefaction was found to be an accessory lobe of the parotid gland.

For convenience, the authors make a clear-cut classification of tumefactions which may occur in the parotid salivary gland, and present examples of each:

1. Inflammatory lesions
2. Neoplasms of connective tissue originally arising only incidentally in the parotid gland
   a. Vascular tumors—hemangioma and hemangioendothelioma
   b. Lipoma
   c. Sarcoma
3. Neoplasms of the salivary gland per se
   a. Mixed tumor
   b. Papillary cystadenoma lymphomatosum
   c. Carcinoma
   d. Cylindroma
   e. Mucoepidermoid tumor
4. Miscellaneous—including parotid cyst

This classification indicates in itself the great diversity of possible parotid involvement.

In the body of their paper the authors make available information which may be of use to the practicing physician in the interpretation and management of parotid problems.

Chronic recurrent infection of the parotid gland begins characteristically in childhood. The fibrotic nodular gland which results may be clinically indistinguishable from neoplastic involvement. Microscopic study of the lesion is therefore necessary to make an accurate differential diagnosis. Incisional biopsy is to be preferred, since it has been shown that resection of the parotid gland with chronic inflammatory involvement has resulted in a high percentage of cases with permanent damage to the facial nerve.

Vascular tumors are the typical tumor of the parotid during the first year of life and usually run a benign course. Of the eighteen cases tabulated since 1920, all were initially observed during infancy. Howard and associates report

good therapeutic results in their cases by combining a surgical procedure—biopsy, or partial excision, or excision—with postoperative irradiation.

Neoplasms of the salivary gland per se include several types. The mixed tumor begins most commonly in young adults but occurs also in children. Of 2,309 cases reported in the literature since 1920, sixty-six were found in children. The authors add six cases of their own. The mixed tumor is classified as a nonmetastasizing neoplasm, although local recurrence of the tumor after excision is a common complication. In four of their six cases, followed for nine to forty-four years, postoperative recurrence of the tumor was noted. Repeated surgical excision combined with irradiation gave satisfactory results.

Carcinoma, a less common but more serious involvement of the parotid gland, has been reported to occur in children in twenty-five instances. In eight of these, death was due directly to the tumor and was sometimes associated with distant metastasis. Howard and co-workers describe a patient of their own who was first seen at the age of 15 years. Microscopic study revealed that the tumor was a cylindroma. This type of carcinoma characteristically runs a slow course, is locally invasive, and is known to metastasize late to regional lymph nodes and to the lungs.

Mucoepidermoid tumors are malignant epithelial neoplasms, which include tumors of low-grade malignancy and those having a clinical course similar to the carcinomas. In one instance the parotid tumor was first noted at the age of 4 years and initial surgical excision was carried out at the age of 14 years. Subsequently, recurrent tumors were excised at 24, 27, 40, and 41 years of age; and despite irradiation therapy following the last two operations, the patient finally succumbed to the malignancy at the age of 43 years. An autopsy revealed the presence of metastases in the cervical lymph nodes, in the lungs, and in the retroperitoneal nodes.

The authors summarize a large amount of clinical study by tabulating their material clearly and comprehensively, and presenting objectively the results of therapy. They emphasize that unless the surgeon is aware that the facial nerve pursues a superficial course in infants and young children, he may cause injury before realizing that the dissection is actually in the vicinity of the facial nerve. The authors express preference for incisional biopsy for initial diagnosis since injury may also be done to the facial nerve during the resection of large tumor masses, particularly if the tumefaction is on a chronic inflammatory basis. Radiation therapy is not advocated as a routine procedure in the treatment of parotid tumors. There should be specific indications for its use as a supplement to surgical treatment.

These studies ought to prove valuable reference for the physician confronted with any of the problems considered in this presentation of unusual subject matter.

RUSSELL J. BLATTNER

REFERENCE

1. Howard, J. M., Rawson, A. J., Koop, C. E., Horn, R. C., and Royster, H. P.: Surg., Gynec. & Obst. 90: 307-319, 1950.

PAST PRESIDENTS OF PEDIATRIC SOCIETIES IN THE UNITED STATES

SINCE the Transactions of the American Pediatric Society were discontinued in 1938, and those of the Section on Pediatrics of the American Medical Association in 1931, there have been no lists available of the presidents of the senior pediatric societies. To meet requests for information that frequently came to THE JOURNAL, lists were prepared for office use. To these, lists of the more recently formed national pediatric societies were added from information provided by their secretaries. At the annual meeting of the Editorial Board in May it was decided to publish the lists from the date of origin of the societies to 1950 as a matter of permanent record.

CHAIRMEN OF THE SECTION ON PEDIATRICS OF THE AMERICAN MEDICAL ASSOCIATION

(Founded 1880)

1880 Abraham Jacobi, New York
1881 S. C. Busey, Washington
William Lee, Baltimore
1882 R. F. Blount, Wabash, Ind.
C. W. Earle, Chicago
1883 William Lee, Baltimore
1884 J. H. Pope, Marshall, Texas
1885 W. D. Haggard, Nashville
1886 Delaskie Miller, Chicago
1887 F. E. Waxham, Chicago
1888 J. A. Larrabee, Louisville
1889 I. N. Love, St. Louis
1890 W. P. Watson, Jersey City
1891 E. F. Brush, Mt. Vernon, N. Y.
1892 C. G. Jennings, Detroit
1893 W. S. Christopher, Chicago
1894 E. H. Small, Pennsylvania
1895 A. C. Cotton, Chicago
1896 J. A. Larrabee, Louisville
1897 J. P. Crozer Griffith, Philadelphia
1898 H. E. Tuley, Louisville
1899 E. Rosenthal, Philadelphia
1900 S. W. Kelley, Cleveland
1901 H. M. McClanahan, Omaha
1902 John C. Cook, Chicago
1903 Charles G. Kerley, New York
1904 John L. Morse, Boston
1905 W. C. Hollopeter, Philadelphia
1906 J. Ross Snyder, Birmingham
1907 E. E. Graham, Philadelphia
1908 Thomas Southworth, New York
1909 William J. Butler, Chicago
1910 Samuel McC. Hamill, Philadelphia
1911 Isaac A. Abt, Chicago
1912 Henry D. Chapin, New York
1913 Frank S. Churchill, Chicago
1914 Lawrence T. Royster, Norfolk
1915 T. C. McCleave, Berkeley
1916 Julius P. Sedgwick, Minneapolis
1917 Laurence R. DeBuys, New Orleans
1918 Frank P. Gengenbach, Denver
1919 Fritz B. Talbot, Boston
1920 Frank C. Neff, Kansas City
1921 E. C. Fleischner, San Francisco
1922 Borden S. Veeder, St. Louis
1923 Henry F. Helmholz, Rochester, Minn.
1924 Edgar J. Huenekens, Minneapolis
1925 Clifford G. Grulee, Chicago
1926 Henry J. Gerstenberger, Cleveland
1927 Hugh McCulloch, St. Louis
1928 William A. Mulherin, Augusta, Ga.
1929 William Weston, Columbia, S. C.
1930 Charles A. Aldrich, Winnetka, Ill.
1931 Jay I. Durand, Seattle
1932 Fred W. Schlutz, Chicago
1933 Alfred A. Walker, Birmingham
1934 A. Graeme Mitchell, Cincinnati
1935 Horton Casparis, Nashville
1936 Ralph M. Tyson, Philadelphia
1937 Clifford D. Sweet, Oakland, Calif.
1938 Edward C. Mitchell, Memphis
1939 Albert D. Kaiser, Rochester, N. Y.
1940 Julius H. Hess, Chicago
1941 Philip M. Stimson, New York
1942 Hugh L. Dwyer, Kansas City
1943 No meeting
1944 John Aikman, Rochester, N. Y.
1945 No meeting
1946 Gilbert Levy, Memphis
1947 Oscar Reiss, Los Angeles
1948 Woodruff L. Crawford, Rockford, Ill.
1949 Margaret M. Nicholson, Washington, D. C.

PRESIDENTS OF THE AMERICAN PEDIATRIC SOCIETY

(Founded 1888)

1889	Abraham Jacobi, New York
1890	Job L. Smith, New York
1891	Thomas M. Rotch, Boston
1892	William Osler, Baltimore
1893	Alexander D. Blackader, Montreal
1894	John M. Keating, Colorado Springs
1895	Frederick F. Forchheimer, Cincinnati
1896	Joseph O'Dwyer, New York
1897	Samuel S. Adams, Washington
1898	L. Emmett Holt, New York
1899	William P. Northrup, New York
1900	Henry E. Koplik, New York
1901	William D. Booker, Baltimore
1902	Walter S. Christopher, Cincinnati
1903	J. P. Crozer Griffith, Philadelphia
1904	August Caillé, New York
1905	Charles G. Jennings, Detroit
1906	Abraham Jacobi, New York
1907	Benjamin K. Rachford, Cincinnati
1908	Charles G. Kerley, New York
1909	Charles P. Putnam, Boston
1910	David L. Edsall, Philadelphia
1911	Henry D. Chapin, New York
1912	Walter L. Carr, New York
1913	John L. Morse, Boston
1914	Samuel McC. Hamill, Philadelphia
1915	George N. Acker, Washington
1916	Rowland G. Freeman, New York
1917	Frank S. Churchill, Chicago
1918	Linnaeus E. La Fétra, New York
1919	Edwin E. Graham, Philadelphia
1920	Thomas S. Southworth, New York
1921	John Howland, Baltimore
1922	Maynard Ladd, Boston
1923	L. Emmett Holt, New York
1924	David M. Cowie, Ann Arbor
1925	John Ruhräh, Baltimore
1926	J. H. Mason Knox, Jr., Baltimore
1927	Isaac A. Abt, Chicago
1928	John C. Gittings, Philadelphia,
1929	Henry L. K. Shaw, Albany
1930	Joseph Brennemann, Chicago
1931	Philip Van Ingen, New York
1932	Howard C. Carpenter, Philadelphia
1933	Oscar M. Schloss, New York
1934	Charles A. Fife, Philadelphia
1935	Borden S. Veeder, St. Louis
1936	Fritz B. Talbot, Boston
1937	Henry F. Helmholz, Rochester, Minn.
1938	Kenneth D. Blackfan, Boston
1939	Clifford G. Grulee, Evanston, Ill.
1940	Herbert Wilcox, Oxford, N. H.
1941	Thomas B. Cooley, Detroit
1942	Edwards A. Park, Baltimore
1943	James L. Gamble, Brookline
1944	No meeting
1945	C. A. Aldrich, Rochester, Minn.
1946	Harold K. Faber, San Francisco
1947	Grover Powers, New Haven, Conn.
1948	Jean V. Cooke, St. Louis
1949	Philip C. Jeans, Iowa City
1950	Bronson Crothers, Boston

PRESIDENTS OF THE SOCIETY FOR PEDIATRIC RESEARCH

(Founded 1929)

1929-1931	James L. Gamble, Boston
1931-1932	L. A. Hoag, New York
1932-1933	Bengt L. K. Hamilton, Chicago
1933-1934	Rustin McIntosh, New York
1934-1935	Joseph Stokes, Jr., Philadelphia
1935-1936	Charles F. McKhann, Cleveland
1936-1937	Francis S. Smyth, San Francisco
1937-1938	Samuel Z. Levine, New York
1938-1939	L. E. Holt, Jr., New York
1939-1940	Daniel C. Darrow, New Haven
1940-1941	A. Ashley Weech, Jr., Cincinnati
1941-1942	George M. Guest, Cincinnati
1942-1944	Joseph A. Johnston, Detroit
No meeting in 1943	
1944-1946	Edward M. Bridge, Buffalo
No meeting in 1945	
1946-1947	Mitchell I. Rubin, Buffalo
1947-1948	Donovan J. McCune, New York
1948-1949	Sidney Farber, Boston
1949-1950	Francis F. Schwentker, Baltimore

PRESIDENTS OF THE AMERICAN ACADEMY OF PEDIATRICS

(Founded 1930)

1930	Isaac A. Abt, Chicago
1931	John L. Morse, Boston
1932	Samuel McC. Hamill, Philadelphia
1933	John Ruhräh, Baltimore
1934	Thomas B. Cooley, Detroit
1935	Henry Dietrich, Los Angeles
1936	Laurence R. DeBuys, New Orleans
1937	Philip Van Ingen, New York
1938	Henry F. Helmholz, Rochester, Minn.
1939	Joseph B. Bilderback, Portland, Ore.

1940	Richard M. Smith, Boston	1946	Lee Forrest Hill, Des Moines
1941	Edward C. Mitchell, Memphis	1947	John A. Toomey, Cleveland
1942	Borden S. Veeder, St. Louis	1948	Warren R. Sisson, Boston
1943	Franklin P. Gengenbach, Denver	1949	Edward B. Shaw, San Francisco
1944	Joseph S. Wall, Washington	1950	Paul W. Beaven, Rochester, N. Y.
1945	Jay I. Durand, Seattle		

AMERICAN BOARD OF PEDIATRICS
(Founded 1933)

1933-1941	Borden S. Veeder, St. Louis	1945-1947	Charles Anderson Aldrich, Rochester, Minn.
1941-1943	Horton Casparis, Nashville	1947-1950	Charles F. McKhann, Cleveland
1943-1945	Edward B. Shaw, San Francisco		

News and Notes

The Harvard Medical School announces an intensive graduate course in Pediatric Endocrinology and Metabolic Disease, Oct. 2 to 7, 1950, 9:00 A.M. to 4:30 P.M., daily, by Dr. N. B. Talbot and Staff, Children's Medical Service, Massachusetts General Hospital. For details, write Courses for Graduates, Harvard Medical School, Boston, Mass.

Book Reviews

Child Growth and Development. Elizabeth B. Hurlock, New York, 1949, McGraw-Hill Book Company, Inc., 368 pages. Price $3.50.

This book was written by a psychologist and covers in a simple fashion some of the practical aspects of the growth and development of the child. For example, it describes such things as layette needs, methods of feeding, and the common problems of growth and development. Such situations are described in a very simple, mechanistic manner with comparatively little appreciation of the complex emotional situations that arise in the child-parent relationship. It is the kind of book that might be of some help to the not-too-anxious mother preparing for her first child.

S. R. WARSON

Child Development. Willard C. Olson, Boston, 1949, D. C. Heath & Co., 398 pages. Price $4.00.

Dr. Olson is a person with considerable experience in the field of educational psychology. His present volume is concerned with child development as it relates to the field of education. The volume is a comprehensive one which includes contributions to an understanding of development from many different points of view. It also includes a great deal of research data and good bibliographies. The book should be of special value to pediatricians and others who are active in the field of education.

S. R. WARSON

Streptomycin and Dihydrostreptomycin in Tuberculosis. Edited by H. McLeod Riggins, M.D., and H. Corwin Hinshaw, M.D., New York, 1949, National Tuberculosis Association, 554 pages.

Fifty-eight contributors have collaborated in the preparation of this comprehensive discussion of the effect of these antibiotics upon tuberculosis. The book is divided into nine sections, each of which contains from one to nine complete reports by investigators upon those phases of the subject in which they have made careful observations. Beginning with a recounting of the first official announcement by Albert Schatz and Selman A. Waksman of the in vitro bacteriostatic action of streptomycin against the *Mycobacterium tuberculosis*, chapters dealing with the effects of streptomycin on experimental tuberculosis in guinea pigs by Feldman and Hinshaw, and streptomycin in the treatment of clinical tuberculosis by Hinshaw and Feldman follow.

The second section of the book deals with a description of the streptomycin-tuberculosis research project of the American Trudeau Society and contains important conclusions which were drawn from this investigation. This is followed by a comprehensive discussion of some of the bacteriologic problems in relation to the chemotherapy of tuberculosis in the third and fourth sections. Here, methods of determination of streptomycin sensitivity, a thorough consideration of the pathology of tuberculosis in relation to chemotherapy, the preclinical evidence of the modifying effect of streptomycin on the tuberculous lesions of guinea pigs which led to subsequent clinical trials in human beings, and the effect of streptomycin on the histopathologic aspects of tuberculosis are recorded.

The subject of streptomycin in the treatment of tuberculosis is thoroughly covered by the nine comprehensive reports of the American Trudeau Society Investigators in Section V, and then is followed by a summary report on the streptomycin-tuberculosis research project of the American Trudeau Society in Section VI.

The toxicity of streptomycin for the auditory and vestibular mechanisms, the effect of streptomycin on the function of the eighth nerve, streptomycin in bone and joint tuberculosis, and the report of the Veterans Administration on streptomycin in the treatment of tuberculosis are discussed in Section VII.

The remainder of the book records important experimental and clinical studies which have been carried out in the investigation of dihydrostreptomycin in Section VIII and the clinical studies of combined chemotherapy in tuberculosis in Section IX. Included in the latter are observations upon the effect of para-aminosalicylic acid in preventing acquired resistance to streptomycin by the *Myco. tuberculosis* and the effect of combined therapy with streptomycin, para-aminosalicylic acid, and Promin on the emergence of streptomycin-resistant strains of tubercle bacilli.

Free use is made of charts and illustrations, including some excellent reproductions of radiograms of the chest, photographs of bacterial cultures, and photomicrographs. The work is most complete and affords a clear and concise presentation of our present knowledge of the effects of the antibiotics upon tuberculosis. It should find wide acceptance by the medical profession at large because of its usefulness as a reference book.

Nursery School Guide. Rhoda Kellogg, Boston, 1949, Houghton Mifflin Company, 490 pages. Price $4.00.

Mrs. Kellogg is a person long experienced in the field of nursery school education. Her book covers in a very thorough manner the concepts of such education and the equipment and staff that have been found to be useful in carrying it out. The book should be very helpful to anyone who is thinking of starting a nursery school.

S. R. WARSON

Editor's Column

THE ANTIHISTAMINIC DRUGS AND THE COMMON COLD

REGARDLESS of what the final verdict turns out to be, the story of the antihistaminic drugs and the common cold will furnish a most intriguing episode to the medical historian who writes of the years 1949-1950. There are three phases to the episode. The first and third follow the usual pattern of procedure which has been repeated hundreds of times. A new method of treatment or drug is introduced which in someone's hands has seemed to be of value. It is then tried out independently by others and the original claims are confirmed or disapproved. The intelligent practitioner watches the procedure with interest, but waits until a definite evaluation is made before adding it to his own therapeutic armamentarium. Again and again a suggested drug has been found to be of little value and the incident forgotten.

In this particular incident a second intermediate phase was injected which is almost without precedent. Moreover, this second phase highlights some of the more striking changes that have been developing in the relationship of the physician to the public, the conflicting ethics of technical and lay journalism, the power and shortcomings of government bureaus, and the commercial use of the press and radio to promote the sale of drugs of dangerous and questionable value. It is this aspect that will make the episode of intense interest to the historian of the future, as it mirrors some of the differences that exist at the present time between medical ethics and attitudes, and those of the public. The episode would not have occurred had it not been that the disease involved was the "common cold," that pestiferous scourge of mankind with a case rate of 400,000,000 a year. This was the factor that makes it understandable as well as possible to have occurred.

* * * * *

Brewster,[1] accepting the theory that the manifestations of the common cold in its early stage are allergic in nature, started to use antihistaminic drugs in the treatment of colds at the Great Lakes Naval Training Station. In 1947, and again in 1949, he reported favorably on their use and emphasized the importance of early treatment, as the benefits decreased with the length of time elapsing between the onset of the cold and the beginning of medication. He had no valid controls, and the diagnosis of the "cold" was largely subjective. Quite logically, the use of antihistaminic drugs was then taken up by a number of physicians in large manufacturing plants where the common cold is the greatest cause of loss of time from illness. Teabrock,[2] Philips and Fishbein,[3] and Murray[4] reported favorably on their use in industrial plants. Murray stated they gave more relief, better results, and more so-called "cures" than any other treatment used in the past twenty-eight years, but did not give comparative figures or detail the other methods of treatment. In

these reports the diagnosis was almost entirely subjective and the controls unsatisfactory. All emphasized the importance of use at the beginning of a cold.

The real impetus came from the report of Armino and Sweet[5] who studied the use of antihistaminic drugs in three institutions—a penitentiary, a convent, and a seminary, with a total population of 3,000. It was an ideal situation for a study as the population was under control and close medical supervision, and the opportunity for exposure to infection was the same for both study and control groups. The absence of this last factor is one of the great weaknesses of the other studies on the subject. A group of 300 was given an antihistamine daily for 180 days. One hundred received 50 mg. daily, a second one hundred were given 50 mg. b.i.d., and the remaining one hundred 50 mg. t.i.d. A group of 300 receiving a placebo were used as controls. Of those receiving the drug 265 (88 per cent) remained free from symptoms of a cold, as contrasted with 59 (17.7 per cent) receiving the placebo. As the subjects were all under control and constant medical supervision these results are statistically significant. They also concluded from their treatment studies made on others in the institutions that excellent results were obtained if the drugs were given in an early stage of a cold. The youngest patient in their study was 18 years of age. Looking at it unemotionally, at this stage enough evidence was at hand to warrant further careful controlled studies of a treatment that looked promising.

* * * * *

Then came the deluge. In the past the public has usually awaited the judgment of the medical profession before accepting a "cure." But in this case, before the report of Armino and Sweet was available to physicians, a lay magazine obtained information about the study, and the notorious article, "Is This, at Last, Good-bye to the Common Cold" was published in the December, 1949, issue. In view of what followed, the only charitable thing that can be said of the publishers giving widespread publicity to a toxic drug whose value in the common cold was not as yet proved is that they were not instigated by motives of advertising profits. For physicians it was a hectic time—dozens of telephone calls a day from patients wanting "some of the new cold medicine." The pediatricians were perhaps more fortunate than other physicians as they could reply that the drug had not as yet been tried out in children for colds, and that when used for other conditions there were often side reactions that were bad for children.

Then the situation worsened. The Government Food and Drug Administration released antihistaminic drugs, known to be toxic to many individuals, for open over-the-counter sale. Whether this action was due to commercial pressure, or to limited legal powers, we do not know, but whatever the reason, it permitted a situation to develop that in the opinion of physicians was inimical to the public health and welfare. For days on end full page advertisements of a "cure" for colds appeared in the newspapers, and one could scarcely turn on the radio without being greeted by a "commercial" extolling one or another antihistaminic drug sold by this or that company. We are

glad to be able to say that most of the pharmaceutical firms who had been making antihistaminic drugs for a number of years restrained from cashing in on the "easy money." The advertising claims became so bad that the Federal Trade Commission stepped in, and in June, 1950, five firms which were the chief offenders agreed to stop advertising the drugs as a "cure," or "preventive" of colds, in order to escape prosecution for false advertising claims.

This second phase is almost without parallel in medical history. The Council on Pharmacy of the A. M. A. issued a statement[6] to the profession urging caution and considered the claims as unproved. The Committee on Child Welfare of the Medical Society of the County of New York reviewed the subject[7] and stressed the danger of the toxicity of the antihistaminic drugs for children. They cited two accidental deaths from their ingestion. Every pediatrician who uses the drugs for allergic conditions warns the parents that the usual doses are toxic for some children and produce side results. THE JOURNAL received several manuscripts dealing with their use for colds in children. In all, the results were based on the opinion of the mother, and there were no controls. Naturally none were approved by the Editorial Board for publication.

* * * * *

We now reach the third phase of the episode which ordinarily would have been the second. Other investigators are making independent studies and in recent reports the value of the antihistaminic drugs is not so promising. Hoagland and his associates[8] at West Point (is this another Army-Navy feud?) studied 190 cases of colds. Two groups were given antihistamine orally and one by nebulizer, while two control groups were given placebos. They could find no significant differences in the proportion of patients helped, and the same proportion of patients reported no benefit from the drug as from the placebo. A total of one hundred ninety cases divided into five groups is small for their findings to be of much statistical significance. Cowan and Diehl[9] studied the prophylactic value in a group of 367 volunteer students at the University of Minnesota. Some 980 colds were reported in the group between December, 1948, and April, 1949. Very little difference was found between the tested and control groups as to the severity of the colds and their duration. Feller and his associates[10] in Cleveland could find no beneficial or therapeutic effects of the antihistamines on naturally occurring colds in a group of families under observation, and in two small groups of volunteers inoculated with nasal secretions of patients with common colds. In all of these unfavorable reports, the numbers are small, and there is no evidence presented that the opportunity for exposure to infection was the same for the test and control groups.

* * * * *

So the matter stands at the present time. Seemingly much of the difficulty lies in defining the "common cold," and the question arises whether the various studies were considering the same thing. While most consider the "cold" as a virus infection from its course and epidemiology, a specific virus is as yet un-

proved. By analogy with some other diseases due to a virus, if it is viral in nature, there must be a multitude of strains to account for the seasonal variations in severity and course. Some, furthermore, who have studied the cold extensively question a virus as the cause. Certainly the strictures laid down by the Council on Pharmacy of the A. M. A. as to diagnosis in studying the effect of the antihistamines on colds are rather impractical in our present state of knowledge and laboratory facilities. So far as children are concerned, it would be wise for the practitioner to hold off and discourage the use of antihistamines until such time as they have been thoroughly tested with controls. Large resident children's institutions, where the exposure factor is the same for both tested and control groups, and where there is close medical supervision, seemingly offer the only satisfactory environment for a scientific study to determine whether or not the antihistamines are of value in preventing and treating colds in children. If a "wish thought" could make them of value, we would all be using them.

B. S. V.

REFERENCES

1. Brewster, J. M.: U. S. Nav. M. Bull. **47**: 810, 1947.
—: Ibid. **49**: 1, 1949.
2. Teabrock, H. E.: Indust. Med. **19**: 39, 1950.
3. Philips, W. F. P., and Fishbein, W. I.: Indust. Med. **18**: 526, 1949.
4. Murray, H. G.: Indust. Med. **18**: 215, 1949.
5. Armino, J. J., and Sweet, C. C.: Indust. Med. **18**: 509, 1949.
6. J. A. M. A. **142**: 566, 1950.
7. New York Medicine, Feb. 5, 1950.
8. Hoagland, R. J., Dietz, E. N., Myers, P. W., and Cosand, H. C.: J. A. M. A. **143**: 157, 1950.
9. Cowan, D. W., and Diehl, H. S.: J. A. M. A. **143**: 421, 1950.
10. Feller, A. E., Badger, G. F., Hodges, R. G., Jordon, W. S., Jr., Rammelkamp, C. H., Jr., and Dingle, J. H.: New England J. Med. **242**: 737, 1950.

SUPPLEMENT ON DIABETES

ONE of the most difficult fields of medical writing is the preparation of articles of a scientific nature for distribution to and use by patients. We are not referring to the innumerable articles on general information appearing in the newspapers and popular magazines, or propaganda articles published by many organizations. From time to time an article of the type we refer to comes to light from some clinic where it has been worked over and used for several years, and is distributed in mimeographed form. It serves a most important function but hardly belongs with the type of material usually published in a medical journal. An example is a discussion of diabetes for parents in use at the diabetic clinic at the St. Louis Children's Hospital. The Editorial Board of THE JOURNAL believes this article will be of great help to other clinics and pediatricians in practice, and therefore decided to publish it as a supplement to a regular issue of THE JOURNAL.

The publishers of THE JOURNAL, The C. V. Mosby Company, anticipating a demand for reprints, will have a quantity printed to be available at $3.75 a hundred, f.o.b. St. Louis. Orders for reprints should be addressed to The C. V Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo.